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Water Metabolism and Fluid Compartment Volumes in Humans at Altitude

A Compendium of Research (1914–1996)

J. L. Chou, N. J. Stad, E. Gay, G. I. West, P. R. Barnes, and J. E. Greenleaf

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Summary

This compendium includes abstracts and synopses of clinical observations and of more basic studies involving physiological mechanisms concerning interaction of water metabolism and fluid compartment volumes in humans during altitude exposure. If the author's abstract or summary was appropriate, it was included. In other cases a more detailed synopsis of the paper was prepared under the subheadings Purpose, Methods, Results, and Conclusions. Author and subject indices are provided, plus an additional selected bibliography of related work and of those papers received after the volume was being prepared for publication. This volume includes material published from 1914 through 1995.

Introduction

The purpose of this compendium is to present summaries of clinical observations and results from more basic studies that help to elucidate physiological mechanisms for control of water balance and fluid compartment volumes at altitude in humans. If the author's abstract or summary was appropriate, it was utilized. In some cases a more detailed synopsis was provided under the subheadings Purpose, Methods, Results, and Conclusions.

This volume includes studies published from 1914 through 1995. Author and subject indices are provided. The material is listed in alphabetical order by first author and numbered consecutively by abstract number, not page number.

We thank our many colleagues who sent us reprints, and apologize to those whose work we have inadvertently overlooked.

The authors thank Esther Johnson for valuable technical assistance.

J.E.G.

1. Abbrecht PH and JK Littell.

Plasma erythropoietin in men and mice during acclimatization to different altitudes.

Journal of Applied Physiology 32:54-58, 1972.

Authors' Abstract

Repeated measurements of plasma erythropoietin concentration were made in five men before and during 10 days stay at 14,300 ft. Serial determinations of plasma erythropoietin concentration over a 10-day period were also made in mice during exposure to air pressures of 510, 440, or 360 mm Hg, equivalent to altitudes of 10,500, 14,500, and 19,000 ft, respectively. Calibration curves using a standard erythropoietin preparation were done with all assays, so that erythropoietin concentration could be expressed in standard units per milliliter. In human beings, erythropoietin concentration reached maximum values from 19- to 39-hr hypoxia, and then decreased rapidly without a significant change in hematocrit or blood hemoglobin concentration. Maximum erythropoietin values in mice were measured at 12- to 18-hr hypoxic exposure, with the earlier peak occurring at the highest altitude. In all cases, erythropoietin concentration had decreased to values not significantly different from prehypoxic control values by the 10th day at altitude. There was good correlation between maximum erythropoietin concentration and estimated PO_2 in mice.

2. Alexander JK, LH Hartley, M Modelski and RF Grover.

Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude.

Journal of Applied Physiology 23:849-858, 1967.

Authors' Abstract

The cardiac output response to submaximal supine leg exercise was determined in eight normal subjects, first at sea level and again after 10 days at 3,100 m. Using the direct Fick method for oxygen, cardiac output was measured at rest and during four work loads requiring oxygen uptakes of 600-1,600 ml/min at both altitudes. At rest and at each level of exercise, cardiac output was less at 3,100 m, by as much as 2 liters/min. Reduced cardiac output was chiefly due to decrease in stroke volume. Though blood volume was less at high altitude, acute plasma volume expansion with dextran in two subjects failed to restore stroke volume to sea-level values. The reduction of stroke volume was apparently not a result of altered blood pH, pulmonary hypertension and right ventricular overload, depletion of myocardial norepinephrine stores, diminished sympathetic nervous activity, or reduction in blood volume and ventricular filling pressures. Myocardial function was probably depressed by hypoxia secondary to lowered coronary arterial oxygen tension, reduced coronary blood flow, or both.

3. Anand IS, Y Chandrashekhar, SK Rao, RM Malhotra, R Ferrari, J Chandana, B Ramesh, KJ Shetty and MS Boparai.

Body fluid compartments, renal blood flow, and hormones at 6,000 m in normal subjects.

Journal of Applied Physiology 74:1234-1239, 1993.

Authors' Abstract

We previously described a syndrome of congestive heart failure occurring in healthy young men at extreme altitude (Anand et al. *Lancet* 335: 561-565, 1990). The pathogenesis of this condition is unclear. We therefore measured body fluid compartments, renal blood flow, and a variety of plasma hormones in 10 asymptomatic young men staying above 6,000 m for > 10 wk and compared the results with controls at sea level. Body compartments were measured with isotope dilution techniques and renal blood flow with *o*-[^{125}I]iodohippurate sodium. There was a marked expansion of all the fluid spaces: total body sodium was 14% above normal ($P<0.05$), total body water was 18% above normal ($P<0.05$), plasma volume was 33% above normal ($P<0.05$), and blood volume was 84.5% above normal ($P<0.001$). The effective renal plasma flow was lower than normal by 55% ($P<0.001$), but the reduction in the effective renal blood flow was 37% below normal ($P<0.001$) because the hematocrit was high (41.6% above normal). Plasma norepinephrine was nearly 3 times normal ($P<0.01$), cortisol 3 times normal ($P<0.001$), and growth hormone 18 times normal

(P<0.01). Aldosterone was twice normal (P<0.03). Plasma epinephrine, atrial natriuretic peptide, and plasma renin activity were unchanged. The degree of fluid retention in these normal subjects was similar to that in patients with severe untreated congestive heart failure (Anand et al. *Circulation* 80:299-305, 1989), whereas sodium retention and reduction in effective renal blood flow were less. Serum aldosterone was less in our normal subjects than in patients with congestive heart failure. Our findings suggest that a prolonged stay at extreme altitude can cause salt and water retention to an extent approximately similar to that in untreated congestive heart failure. It is likely that the stress of hypobaric hypoxia, cold, and exertion at high altitude increases catecholamines, which reduce renal blood flow and lead to a congestive state in normal subjects at extreme altitude.

4. **Anderson RJ, RG Pluss, AS Berns, JT Jackson, PE Arnold, RW Schrier and KM McDonald.** Mechanism of effect of hypoxia on renal water excretion. *Journal of Clinical Investigation* 62:769-777, 1978.

Authors' Abstract

The effect of lowering the pressure of oxygen from 80 to 34 mm Hg was examined in anesthetized dogs that were undergoing a water diuresis. This degree of hypoxia was associated with an antidiuresis as urine osmolality (U_{osm}) increased from 107 to 316 mosmol/kg H_2O (P<0.001) and plasma arginine vasopressin increased from 0.06 to 7.5 μU/ml, (P<0.05). However, hypoxia was not associated with significant changes in cardiac output (CO, from 4.2 to 4.7 liters/min), mean arterial pressure (MAP, from 143 to 149 mm Hg), glomerular filtration rate (GFR, from 46 to 42 ml/min), solute excretion rate (SV, from 302 to 297 mosmol/min), or filtration fraction (from 0.26 to 0.27, NS). Hypoxia was associated with an increase in renal vascular resistance (from 0.49 to 0.58 mm Hg/ml per min, P<0.01). The magnitude of hypoxia-induced antidiuresis was the same in innervated kidneys and denervated kidneys. To further examine the role of vasopressin in this antidiuresis, hypoxia was induced in hypophysectomized animals. The effect of hypoxia on CO, MAP, GFR, SV, and renal blood flow in hypophysectomized animals was the same as in intact animals. In contrast to intact animals, however, hypoxia did not induce a significant antidiuresis in hypophysectomized animals (U_{osm} from 72 to 82 mosmol/kg H_2O). To delineate the afferent pathway for hypoxia-stimulated vasopressin release, hypoxia was induced in dogs with either chemo- or barorecptor denervation. The effect of hypoxia on CO, MAP, GFR, SV, and renal blood flow in the denervated animals was the same as in nondenervated animals. Hypoxia resulted in an anti-diuresis in chemoreceptor (U_{osm} from 113 to 357 mosmol/kg H_2O, P<0.001) but not in baroreceptor (U_{osm} from 116 to 138 mosmol/kg H_2O, NS) denervated animals. To determine if hypoxia alters renal response to vasopressin, exogenous vasopressin was administered to normoxic and hypoxic groups of dogs. The antidiuretic effect of vasopressin was no different in these two groups. These results demonstrate that hypoxia induces an antidiuresis which is independent of alterations in CO, MAP, SV, filtration fraction, renal nerves, or renal response to vasopressin and occurs through baroreceptor-mediated vasopressin release. The nature of the baroreceptor stimulation remains to be elucidated.

5. **Antezana A-M, J-P Richalet, I Noriega, M Galarza and G Antezana.** Hormonal changes in normal and polycythemic high-altitude natives. *Journal of Applied Physiology* 79:795-800, 1995.

Authors' Abstract

Acute and chronic exposure to high-altitude (HA) hypoxia inhibits the renin-angiotensin-aldosterone system and may modify the release of atrial natriuretic peptide (ANP) in sea-level (SL) natives. In HA natives, the release of these hormones could be influenced by changes in blood volume or pulmonary arterial pressure. Twenty-four men residing in La Paz, Bolivia, at 3,600 m were separated into two groups: one normocythemic (HAN; with hematocrit < 57%; n = 13) and the other polycythemic (HAP; with hematocrit > 57%; n = 11). A control group of 9 SL residents was studied in normoxia (SLN) as well as after 4 days spent at 4,350 m (SLH). The groups were tested for plasma active renin (PAR), plasma aldosterone concentration, ANP, and potassium and norepineprine concentrations at rest and after a maximal exercise. Pulmonary arterial systolic pressure was assessed by a Doppler technique. It was observed that PAR and plasma aldosterone concentration at rest and after exercise were lower in the SLH than in the SLN group. PAR and norepineprine concentration were higher among highlanders than in the SLN group. Renin response to exercise was normal among the HAN group and slightly decreased among the HAP group, and an exercise-induced increase in aldosterone was attenuated in both HA groups. Aldosterone response to renin was maintained among the SLH group but was attenuated in the HA groups, possibly owing to a protective mechanism against salt and water retention. Resting and exercise ANP was lower in the HA groups than in the SLN group. In the HAP group, a positive relationship was found between ANP and pulmonary arterial pressure at rest. Evidence of lower plasma ANP in HA natives despite higher pulmonary pressure could be explained by an adaptation to chronic distension of atrial stretch receptors involved in central blood volume regulation.

6. Aoki VS and SM Robinson.
Body hydration and the incidence and severity of acute mountain sickness.
Journal of Applied Physiology 31:363-367, 1971.

Authors' Abstract

The possible influence of the state of body hydration on the development of acute mountain sickness (AMS) was suggested by the reports that diuretics, such as acetazolamide and furosemide, prevented or relieved the symptoms. To study this possibility, 12 subjects were exposed to altitude during 3 separate sessions 2 weeks apart. Each session consisted of 3 days at sea level and 2 days at a simulated altitude of 14,000 ft. At sea level, water deficits were corrected with an oral water load. The subjects were then given either 1) placebo, 2) vasopressin-in-oil to maintain hydration, or 3) furosemide to produce moderate dehydration. Symptom questionnaires and a digit-symbol substitution test (DSST) were administered 4 times daily. At sea level, a significant decrease in body weight with furosemide did not affect symptom or DSST scores. All subjects reported an increase in symptoms at altitude. Although the state of body hydration was significantly different after furosemide treatment, the severity of symptoms and DSST scores were the same as in the other groups.

7. Arnaud J, N Gutierrez, GW Tellez and H Vergnes.
Haematology and erythrocyte metabolism in man at high altitude: An Aymara-Quechua comparison.
American Journal of Physical Anthropology 67:279-284, 1985.

Authors' Abstract

In the course of haematological and biological investigations among Aymara and Quechua populations in Bolivia, an anthropological study of the erythrocytary respiratory function was carried out on the two groups at two altitudes: 3,600 m and 450 m.

A difference in the intensity of the biological variations of the two populations is observed at high altitude.

In the Quechuas, as in any lowland native, the adaptative phenomena are totally and quickly reversible.

In the Aymaras, we detected the existence of more marked haematological and biochemical characters: moderate polycythemia, hyperhaemoglobinemia, microcytosis, metabolical hyperactivity with accumulation of 2-3 di-phosphoglycerate and ATP, and methaemoglobinemia with a drop in the activity of the methaemoglobin reductases. The Aymaras preserve some of those characters (methaemoglobinemia excepted) when they settle in lowlands.

8. Arnaud J, JC Quilici, N Gutierrez, J Beard and H Vergnes.
Methaemoglobin and erythrocyte reducing systems in high-altitude natives.
Annals of Human Biology 6:585-592, 1979.

Authors' Summary

The stress of chronic hypobaric hypoxia present at high altitudes induces a series of adaptive changes in the intermediate

metabolism in erythrocytes of high-altitude natives. Aymaras of the high Andean Plateau are shown to have within erythrocytes: (a) increased activity of $NADH_2$ (GAPDH) generating stages, (b) decreased activity of $NADH_2$ (LDH) consuming steps, (c) significantly increased methaemoglobin content, and (d) a large increase in the level of reduced glutathione. These alterations occur also in persons of the same ethnic group residing at low altitude. There is, however, only a moderate elevation of classic haematological parameters (erythrocyte count, haemoglobin and haematocrit) in highland natives. The functional implications of these metabolic changes are discussed with respect to regulation of erythrocyte metabolism.

9. Ashack R, MO Farber, MH Weinberger, GL Robertson, NS Fineberg and F Manfredi.
Renal and hormonal responses to acute hypoxia in normal individuals.
Journal of Laboratory and Clinical Medicine 106:12-16, 1985.

Authors' Abstract

We studied, in normal volunteers, the effects of 1 hour of hypoxia on the concentration of angiotensin-converting enzyme and bradykinins, along with previously measured parameters of renal and endocrine function. Ten men, 18 to 42 years of age, undergoing water diuresis, breathed a low-oxygen mixture (five breathed 10.5% O_2 and five 12% O_2); all breathed 21% O_2 on a control day. Measurements included mean blood pressure and heart rate every 2 to 3 minutes; plasma levels of renin activity, aldosterone, arginine vasopressin, norepinephrine, and bradykinin, and angiotensin-converting enzyme activity, before and at the end of gas breathing; and urine volume (U_v), creatinine, Na^+, and bradykinin concentration. Arterial blood gases and effective renal plasma flow were determined at the end of gas breathing only. Mean values $\pm$ SEM for arterial blood gases with low O_2 were pH 7.39 $\pm$ 0.02, PO_2 46 $\pm$ 2 torr, PCO_2 39 $\pm$ 2 Torr (12 % O_2) and 7.48 $\pm$ 0.01, 35 $\pm$ 1 Torr, 33 $\pm$ 1 Torr (10.5% O_2). Responses were otherwise identical in both groups, and data were combined for analysis. With hypoxia, heart rate and effective renal plasma flow increased significantly, $P< 0.005$; no changes occurred in U_v, urine Na^+ concentration, glomerular filtration rate, plasma or urine bradykinin concentration, serum angiotensin-converting enzyme activity, plasma renin activity, plasma aldosterone concentration, plasma arginine vasopressin concentration, or plasma norepinephrine concentration. Two subjects with hypoxia (PO_2 43 and 36 torr) showed antidiuresis (U_v decreased > 50%), associated with nausea in one and with decreases in mean blood pressure (16% and 21%) and increases in arginine vasopressin levels (50 pg/ml) in both. This study confirms our previous observation that hypoxia in normal individuals has no direct effect on hormonal or renal parameters thought to affect water excretion; increases in plasma arginine vasopressin levels (two subjects) were induced by nausea or hypotension or both. The new data relate to plasma angiotensin-converting enzyme and to plasma and urine kinin levels, none of which was affected by the hypoxic exposure.

10. Asmussen E and FC Consolazio.
The circulation in rest and work on Mount Evans (4,300 m).
American Journal of Physiology 132:555-563, 1941.

Authors' Summary

Two subjects were studied in rest and work during a sojourn of 15 days at the summit of Mt. Evans, Colorado (elev. 4,300 m). In both subjects an increase in the resting cardiac output of about 100 per cent occurred during the first 4 to 5 days, later followed by a return to values still well above sea-level values.

The blood volume decreased considerably the first 3 or 4 days, then increased to a level still below the sea-level values. The percentage O_2-capacity was increased already the first day, presumably as a result of withdrawal of fluid from the blood. Determinations of the total O_2-capacity showed that an increased formation of red cells first occurred after a latency of 4 to 5 days.

In work the cardiac output was considerably higher the first days than later on, but even then it was still higher than at sea-level. The decline in cardiac output after about a week at high altitude is presumably related to the concomitant increase in blood volume and total O_2-capacity.

The chemosensible reflexes were active during the whole sojourn at Mt. Evans. If the acclimatized subjects breathed an air mixture enriched with O_2, the cardiac output both in rest and during work fell to values lower than the corresponding sea-level values.

The findings are discussed and brought into relation with other results on the regulation of the circulation.

11. Asmussen E and M Nielsen.
Studies on the initial increase in O_2 capacity of the blood at low O_2 pressure.
Acta Physiologica Scandinavica 9:75-87, 1945.

Authors' Summary

Determinations of red cell volumes, plasma proteins, blood volumes and water balance were made in a low pressure chamber at 435-450 mm Hg barometric pressure. It was found that the increase in cell volume - and O_2 capacity during the first days at low pressure was due to a diminished plasma volume, and paralleled by an increase in plasma protein concentration. A similar concentration of the blood was found during fasting (40 hours) at normal barometric pressure, but a much greater concentration of the blood was observed when the subjects fasted at low barometric pressure. In two of the three subjects the increased concentration of the blood at low pressure was accompanied by an extra loss of water from the body. From an estimation of the part played by the extracellular water in this loss, it was found, that about one half of the concentration of the blood was caused by loss of extracellular body water. The other part of the concentration of the blood and, in the third subject, the whole extra concentration at low pressure was due to a leaking-out of fluid from the capillaries, presumably caused by the increased capillary blood pressure and an increased permeability of the capillary walls at low O_2 pressure. While the excess filtration out of the blood no doubt is a sign of insufficiency of the capillaries, incidentally increasing the oxygen capacity of the blood, it is difficult to decide whether the excess excretion of water (increased diuresis) is the result of a regulation, serving the oxygen supply, or whether it is due to other causes.

12. Ayres PJ, RC Hurter and ES Williams.
Aldosterone excretion and potassium retention in subjects living at high altitude.
Nature 191:78-80, 1961.

Annotation

Purpose

To observe changes in body electrolyte composition during exposure to high altitude.

Methods

Members of the Middlesex Hospital Medical School High Altitude Physiological Expedition spent 24 days at 14,300 ft.on Mont. Blanc. 24 hr urine collections were made from several subjects. Aldosterone, sodium and potassium contents were determined. During the study the diet of the subjects consisted of dehydrated food stuffs. To establish the effect of the diet on the results, a one-subject control experiment was conducted at sea level.

Results

Urine analysis showed a drop in aldosterone and potassium excretion in the days immediately following ascent, along with an increase in Na^+ excretion which tended to return to normal values with time.

Conclusion

Changes in body electrolyte composition showed a marked acclimatization effect.

13. Baertschi AJ, J-H Jiao, DE Carlson, RW Campbell, WG Teague, D Willson and DS Gann.
Neural control of ANF release in hypoxia and pulmonary hypertension.
American Journal of Physiology 259:H735-H744, 1990.

Authors' Abstract

Hypoxia causes the release of atrial natriuretic factor (ANF), but the mechanisms are not yet understood. This study examined the relative contribution of pulmonary arterial hypertension, neural pathways, increased heart rate, or increased atrial size to the ANF response. Alveolar hypoxia [fractional concentration of O_2 in inspired gas (FIO_2) = 0.1] or pulmonary arterial hypertension (25–45 mmHg) was induced for 10 min in four series (n = 4-12 each) of anesthetized, mechanically ventilated pigs. During hypoxia, plasma ANF concentrations increased by 29 ±52 (SE) pg/ml (or 271 ±105%) over baseline (35 ±7 pg/ml; $P<0.01$) (series 1). There was also a significant increase of pulmonary arterial

pressure, heart rate, central venous pressure, and pulmonary capillary wedge pressure. Repeated pulmonary hypertension induced by intravenous air infusion caused a repeated and reversible
125 ±14% increase ($P<0.001$) of plasma ANF, and this response was totally abolished by lesion of the cervical vagosympathetic trunks (series 2). Lesion of these nerves 1 h before hypoxia also decreased the ANF response to hypoxia by 45-58% ($P<0.01$), whereas responses of heart rate and atrial pressures were unchanged (series 3). The ANF response to hypoxia, expressed in percent of baseline, was not affected by 0.2 mg/kg propranolol (PR) (no PR: 145 ±63%; PR: 151 ±82%; not significantly different from series 1 and control, series 3), although the increase in heart rate (no PR: 61±15 beats/min) was almost abolished (PR: 17 ±5 beats/min) (series 4). Hypoxia caused no significant changes in right and left atrial peak volume regardless of propranolol, as measured with an electrical conductance catheter. The results indicate that a new neural reflex of probably pulmonary arterial origin mediates 50% of the ANF response to hypoxia. The remaining ANF response remains to be explored further and cannot be explained by conventional release mechanisms such as atrial stretch and pulsatility alone.

14. Baker PT.
Human adaptation to high altitude. *Science* 163:1149-1156, 1969.

Author's Abstract

The high-altitude areas of South America are in many ways favorable for human habitation, and they have supported a large native population for millennia. Despite these facts, immigrant lowland populations have not become predominant in these areas as in other parts of the New World, and lowlanders experience a number of biological difficulties on going to this region.

In order to learn more about the adaptations which enable the native to survive at high altitudes, an intensive study of a native population is being carried out in the district of Nuñoa in the Peruvian Altiplano. In this area hypoxia and cold appear to be the most unusual environmental stresses. Results to date show a high birth rate and a high death rate, the death rate for females, both postnatal and prenatal (as inferred from the sex ratio at birth), being unusually high. Birth weights are low, while placenta weights are high. Postnatal growth is quite slow relative to the rate for other populations throughout the world, and the adolescent growth spurt is less than that for other groups. The maximum oxygen consumption (and thus the capacity for sustained work) of adult males is high despite the reduced atmospheric pressure at high altitude. All lowland groups brought to this altitude showed significant reductions in maximum oxygen consumption. The Nuñoa native's responses to cold exposure also differ from those of the lowlander, apparently because blood flow to his extremities is high during exposure to cold. The disease patterns are not well known: respiratory diseases appear common, whereas there seems to be almost no cardiovascular disease among adults. Systemic blood pressures are very low, particularly those of individuals living in traditional native fashion. Nutrition appears to be good, but analysis of the nutrition studies is continuing.

The results of theses studies are interpreted as showing that some aspects of the natives' adaptation to high altitudes require lifelong exposure to the environmental conditions and may be based on a genetic structure different from that of lowlanders.

15. Banchero N and JC Cruz.
Hemodynamic changes in the Andean native after two years at sea level. *Aerospace Medicine* 41:849-853, 1970.

Authors' Abstract

Eleven healthy high altitude natives were studied by right heart catheterization in Morococha, Peru, at 4,540 m altitude. They were restudied in Lima, at 150 m, after 2 years of continuous residence at this level. Intravascular pressures and cardiac output were measured at rest and during exercise on a bicycle ergometer at a work load of 300 Kg-m/min/m^2.

A significant decrease in heart rate was observed after two years at sea level ($p<0.01$). Resting cardiac output increased from 3.83 L/min/m^2 at high altitude to 4.45 L/min/m^2 at sea level due to a highly significant increase in stroke index ($p<0.001$). However, no changes

in mean systemic arterial pressure were found at sea level due to a fall in systemic vascular resistance. Pulmonary artery pressure and pulmonary vascular resistance decreased significantly (p<0.001) after 2 years at sea level. At sea level changes in mean pulmonary artery pressure during supine exercise were significantly less that those observed at high altitude but larger than those seen in normal sea level residents. This latter finding appears to be related to incomplete regression of the anatomic characteristics of the pulmonary vasculature.

16. Barer AS and EV Yakovleva.
Changes of the concentration of sodium and potassium ions in the human urine and saliva during elevations in a barochamber to the altitude of 5,000 and 6,000 m.
Bulletin of Experimental Biology and Medicine 53:63-65, 1962.

Authors' Abstract

The method of flame photometry was used for studying the sodium and potassium concentration in the saliva and urine of man elevated in a barochamber to the altitude of 5,000 and 6,000 metres. A definite regularity was noted in the shifts of concentration of the substances studied. The concentration of potassium ions has a tendency to rise, while that of sodium--to drop. In repeated elevations these shifts become more smooth.

17. Bärtsch P, M Maggiorini, W Schobersberger, S Shaw, W Rascher, J Girard, P Weidmann and O Oelz.
Enhanced exercise-induced rise of aldosterone and vasopressin preceding mountain sickness.
Journal of Applied Physiology 71:136-143, 1991.

Authors' Abstract

A possible contribution of exercise to the fluid retention associated with acute mountain sickness (AMS) was investigated in 17 mountaineers who underwent an exercise test for 30 min on a bicycle ergometer with a constant work load of 148 ±9 (SE) W at low altitude (LA) and with 103 ±6 W 4-7 h after arrival at 4,559 m or high altitude (HA). Mean heart rates during exercise at both altitudes and during active ascent to HA were similar. Exercise-induced changes at LA did not differ significantly between the eight subjects who stayed well and the nine subjects who developed AMS during a 3-day sojourn at 4,559 m. At HA, O_2 saturation before (71 ±2 vs. 83 ±2%, P<0.01) and during exercise (67 ±2 vs. 72 ±1%, P<0.025) was lower and exercise-induced increase of plasma aldosterone (617 ±116 vs. 233 ±42 pmol/l, P<0.025) and plasma antidiuretic hormone (23.8 ±14.4 vs. 3.4 ±1.8 pmol/l, P<0.05) was greater in the AMS group, whereas exercise-induced rise of plasma atrial natriuretic factor and changes of hematocrit, potassium, and osmolality in plasma were similar in both groups. In the AMS group, exercise at HA was associated with a fall in mean blood pressure (-13 ±2 vs. 0 ±5 Torr, P<0.05) and a greater rise of plasma norepinephrine (14.6 ±1.6 vs. 8.9 ±1.3 nmol/l, P = 0.01) and adrenocorticotropic hormone (30.9 ±13.8 vs. 7.9 ±2.8 pmol/l, P = 0.07), which most likely accounted for the higher plasma aldosterone and antidiuretic hormone levels after exercise. These results demonstrate that exercise at HA performed at a work load comparable with the efforts of mountaineering results in a hormonal constellation that favors greater water and salt retention in subjects subsequently developing AMS compared with those who stay well.

18. Bärtsch P, N Pfluger, M Audétat, S Shaw, P Weidmann, P Vock, W Vetter, D Rennie and O Oelz.
Effects of slow ascent to 4,559 m on fluid homeostasis.
Aviation, Space, and Environmental Medicine 62:105-110, 1991.

Authors' Abstract

Since acute mountain sickness (AMS) is associated with rapid ascent and with fluid retention, we assessed clinical status and fluid homeaostasis in men slowly ascending on foot over 3 d to 4559 m and remaining at this altitude 5 d. We studied 15 male mountaineers, 6 of whom had previously had repeated, severe AMS or high altitude pulmonary edema (HAPE), at 1170 m, 3611 m, and 4559 m. We found that four of the six subjects with previous AMS or HAPE compared with none of nine with no such history, developed these conditions. Those who remained well had a

diuresis that could not be overcome by increasing fluid intake and no change in renin activity, plasma aldosterone, or atrial natriuretic peptide (ANP). Those who became ill showed considerable weight gain independent of fluid intake, and a great increase in ANP which correlated with measurements of right atrial cross section. We conclude that mountaineers who have previously experienced repeated AMS or HAPE get fluid retention despite slow ascent and that this is associated with widening of the atrium and an increase in ANP.

19. Bärtsch P, S Shaw, M Franciolli, MP Gnädinger and P Weidmann.
Atrial natriuretic peptide in acute mountain sickness.
Journal of Applied Physiology 65:1929–1937, 1988.

Authors' Abstract

To test the hypothesis that elevated atrial natriuretic peptide (ANP) may be involved in altered fluid homeostasis at high altitude, we examined 25 mountaineers at an altitude of 550 m and 6, 18, and 42 h after arrival at an altitude of 4,559 m, which was climbed in 24 h starting from 3,220 m. In 14 subjects, symptoms of acute mountain sickness (AMS) were absent or mild (group A), whereas 11 subjects had severe AMS (group B). Fluid intake was similar in both groups. In group B, urine flow decreased from 61 ±8 (base line) to 36 ±3 (SE) ml/h (maximal decrease) (P<0.05), and sodium excretion from 7.9 ±0.9 to 4.6 ±0.7) mmol l^{-1} h^{-1} (P<0.05); ANP increased from 31 ±4 to 87 ±26 pmol/l (P<0.001), plasma aldosterone from 191 ±27 to 283 ±55 pmol/l (P<0.01 compared with group A), and antidiuretic hormone (ADH) from 1.0 ±0.1 to 2.9 ±1.2 pmol/l (P = 0.08 compared with group A). These variables did not change significantly in group A, with the exception of a decrease in plasma aldosterone from 189 ±19 to 111 ±17 pmol/l (P<0.01). There were no measurable effects of elevated ANP on natriuresis, cortisol, or blood pressure. The reduced diuresis in AMS may be explained by increased plasma aldosterone and ADH overriding the expected renal action of ANP. The significance of elevated ANP in AMS remains to be established. The association of AMS with facial (P<0.005) and pulmonary edema (P<0.05) is compatible with the hypothesis that ANP may contribute to edema formation by its action on transcapillary fluid exchange.

20. Bärtsch P, S Shaw, P Weidmann, M Franciolli, M Maggiorini and O Oelz.
Aldosterone, antidiuretic hormone and atrial natriuretic peptide in acute mountain sickness.
In: Hypoxia and Mountain Medicine. Proceedings of the 7th International Symposium, edited by JR Sutton, G Coates, and CS Houston. New York: Pergamon Press, 1992. p. 73-81.

Annotation

Purpose

Summarizes the major findings of two studies, comparing changes of diuresis and natriuresis with those of plasma levels of aldosterone, antidiuretic hormone and atrial natriuretic peptide between subjects with and without acute mountain sickness upon acute exposure to an altitude of 4,559 m.

Methods

Different subjects participated in the two studies. They were investigated prospectively before ascent and during a sojourn of 3 or 4 days at the high altitude research laboratory located in the Capanna Regina Margherita (4,559 m). The ascent lasted 20-22 h including transportation by cable car from 1,170 to 3,220 m and an overnight stay at 3,611 m. The subjects climbed for 2 h (from 3,220 to 3,611 m) on the first day of ascent and 4-5 h (from 3,611 to 4,559 m) on the second day. In 1986, 25 subjects (age 23–64 y) stayed for 3 days and in 1988, 17 subjects (ages 25-62 y) remained 4 days at 4,559 m; they were examined after 50 min. of rest in the supine position, first at low altitude and 3 times during the stay at high altitude.

In the latter study, an exercise bout of 30 min on a cycle ergometer was performed at low altitude and within 4 to 8 hours after arrival at 4,559 m.

Results

In 1986, 11 of 25 subjects developed acute mountain sickness. Six subjects having acute mountain sickness and two lacking this condition developed high altitude pulmonary edema. In 1988 five cases of high altitude pulmonary edema developed in 9 of the 17 subjects which had acute mountain sickness.

In both studies fluid intake was comparable between the groups with and without acute mountain sickness. In both studies urine output and natriuresis were lower in the groups having acute mountain sickness. In both studies subjects with acute mountain sickness had significantly higher plasma aldosterone at high altitude compared to those without this condition. No statistically significant changes occurred in either group with regard to ADH in plasma or to plasma osmolality. Plasma ANP was significantly elevated in the acute mountain sickness group as compared to non-symptomatic subjects. Plasma levels of renin, norepinephrine and cortisol were also higher in the acute mountain sickness group. However, there were no changes in plasma sodium and adrenocorticotropin levels.

Exercise at high altitude produced significantly higher levels of plasma aldosterone, ADH, renin, norepinephrine, cortisol, and ACTH in the acute mountain sickness group, whereas increases of osmolality, plasma sodium, potassium, protein, and hematocrit were similar in both groups. Mean arterial oxygen saturation prior to exercise was 71 ±3% in the acute mountain sickness group, 83 ±2% in the non-acute mountain sickness group, and fell during exercise to 67 ±2% and 71 ±2%, respectively.

Conclusions

Increased plasma levels of aldosterone at rest and a greater exercise-induced increase of aldosterone and ADH in subjects developing acute mountain sickness may explain their water and salt retention which was independent of the amount of fluid intake. The hormonal alterations favoring enhanced water and salt retention could result from more severe hypoxemia due to decreased ventilatory drive giving rise to stress and hypotensive noradrenergic reactions. Alternatively, the authors cannot exclude that a primary increase in hormonal response to exercise with subsequent fluid retention could lead to interstitial pulmonary edema and account for the observed differences in oxygen saturation. Further investigations are needed to determine the cause and effect relation between changes in hormonal response, alterations in gas exchange and the development of acute mountain sickness.

21. Baylis PH, RA Stockley and DA Heath.
Effect of acute hypoxaemia on plasma arginine vasopressin in conscious man.
Clinical Science and Molecular Medicine 53:401-404, 1977.

Authors' Abstract

1. Acute hypoxaemia has been reported to stimulate vasopressin release in animals.
2. Hypoxaemia induced by breathing 9.3% oxygen for 15-20 min failed to produce a rise in plasma arginine vasopressin concentration in six out of eight healthy human subjects. The two subjects who developed an increase in plasma arginine vasopressin concentration had a significant rise in serum cortisol.
3. Breathing 100% nitrogen until impairment of consciousness caused no rise in plasma arginine vasopressin concentration.

22. Becker EL, JA Schilling and RB Harvey.
Renal function in man acclimatized to high altitude.
Journal of Applied Physiology 10:79-80, 1957.

Authors' Abstract

Studies were carried out at the Andean Institute of Biology, Morococha, Peru (altitude 15,000 ft.) on natives who for generations have been living at high altitude. These acclimatized individuals represent a climato-physiological variety of the human race different from sea level dwellers. The mean data on all subjects showed an 11% decrease in filtration rate, a 52% decrease in effective renal plasma flow, and an 89% increase in filtration fraction, with a 44% increase in hematocrit as compared to normal sea level values taken from the literature.

23. Behm R.
Role of the peripheral arterial chemoreceptors in electrolyte homeostasis and cardiovascular regulation.
In: *Hypoxia and Mountain Medicine. Proceedings of the 7th International Symposium*, edited by JR Sutton JR, G Coates, and CS Houston. New York: Pergamon Press, 1992. p.50-60.

Author's Abstract

In recent years, there has been growing interest in the role of peripheral arterial chemoreceptors in the regulation of sodium homeostasis, especially in hypertensive mammals. Similar morphological, biochemical and functional alterations of arterial chemoreceptors have been described in both hypertensive and hypoxic animals. In normotensive rats, moderate hypobaric hypoxia leads to transient decreases in salt and water intake and slight reductions in arterial blood pressure. In contrast, in spontaneously hypertensive rats, hypoxia induces a sustained suppression of voluntary salt intake and a marked reduction in blood pressure. Water intake is similarly affected by hypoxia in hypertensive and normotensive rats. The effect on salt, but not water intake, is inhibited by carotid body denervation in hypertensive rats. The decrease in blood pressure is attenuated by access to additional dietary salt and augmented by carotid body denervation. Hypoxia is further associated with significant renal sodium retention, although this effect may depend on the salt content of the diet. Hypoxia-induced renal sodium retention is more pronounced in chemodenervated than in intact rats.

These data suggest that peripheral arterial chemoreceptors can play a major role in sodium homeostasis and blood pressure. Presently, the exact mechanisms of interaction between hypoxia and chemoreceptor activation on the one hand and sodium homeostasis and blood pressure on the other hand are not completely understood and warrant further investigations.

24. Berger EY, M Galdston and SA Horwitz.
The effect of anoxic anoxia on the human kidney.
Journal of Clinical Investigation 28:648-652, 1949.

Authors' Abstract

Renal plasma flow in man did not decrease under situations of anoxia where arterial oxygen tension was lowered to about 50 mm Hg. The most pronounced effect of lowered oxygen tension on renal tissue was the increased excretion of sodium and chloride. Anoxic anoxia alone, therefore, does not appear to be the cause of the reduction of renal plasma flow nor the retention of salt and water observed in congestive heart failure.

25. Bharadwaj H.
Effect of prolonged stay at high altitude on body fat content An anthropometric evaluation.
Human Biology 44:303-316, 1972.

Author's Abstract

The effect of 10-months' continuous stay at high altitudes on body fat content was evaluated on troops drawn from two ethnic groups. Body fat content was measured by anthropometric techniques, and it was observed that it declined significantly on prolonged exposure to high altitudes. Since lean body weight increased after exposure to high altitudes, body weight change was much smaller than what had been observed in acute exposures to high altitude by other investigators. Fluctuations in the body fat content at high altitudes could be seasonal.

26. Bharadwaj H, SC Jain and HS Nayar.
Body composition of high altitude natives on descent to the plains: A densitometric, hydrometric, and anthropometric evaluation.
Journal of Applied Physiology 47:65-72, 1981.

Authors' Abstract

Body density was experimentally determined at a field location at 3,920 m on 32 medically fit and active high altitude native males using a water displacement technique. Stature, body weight and the bony widths at the elbow, wrist, knee, and ankles; and thickness of skin folds at eight sites were measured. Based on body density and bony widths, body fat, total body water (TBW), mineral mass and total cell solids (TCS) were calculated.

Similar measurements were made on another group of 16 high altitude natives after one months stay in Dehli (200m). TBW of 11 of these subjects was experimentally determined by the oral administration of 200 Ci of tritiated water. This group of subjects was physically less active in Delhi. At high altitude the natives consumed a balanced diet which provided 20.21 MJ, but in the plains the diet provided only 15.69 MJ though it was nutritionally balanced.

In spite of the reduced calorie intake this group showed greater fat content in Delhi than the group located at high altitude. These men were also hyperhydrated. Hyperhydration of the lean body could be an adaptive response of the high altitude natives to the new environment. Due to the disturbed state of hydration of the lean body of these men in the plains, use of Siri's formula for the computation of total body fat is questioned.

27. Bharadwaj H and MS Malhotra.
Body composition changes after 4 week acclimatization to high altitude: anthropometric and roentgenogrammetric evaluation.
Zeitschrift für Morphologie und Anthropologie 65:285-292, 1974.

Authors' Abstract

Body composition changes were studied by Surks et al. (1966) on subjects abruptly exposed to high altitude (4,300 m) for 8 days. They attributed body weight loss to loss of fat. Though total proteins remained unaltered, the authors noticed significant shifts in proteins from muscle to non-muscle fraction. Hannon et al. (1969) observed reduced thickness of skin folds, and smaller circumferences of the limbs of eight college women exposed to 4,300 m altitude for two and a half months. Consolazio et al. (1968) observed negative nitrogen and water balance after 4-week exposure to 4,300 m altitude, and Krzywicki et al. (1969) have reported losses in body fat, protein, water and mineral contents in subjects exposed for 12 days at the same altitude. Hannon (1969), while reviewing the subject of water balance at high altitude, concluded that there was no hypohydration during brief exposure to high altitude, but only a shift of water from the extra-cellular into the intracellular space. This view has, however, been recently contradicted by Krzywicki et al. (1971) who observed 2.25 kg water loss during 6-day exposure to 4,300 m altitude. Significant water loss took place exclusively from the intracellular space, whereas extracellular space increased significantly.

In view of these conflicting results adaptive changes in body composition have been studied on lowlanders at altitudes ranging 3962 to 4115 m, after 4 weeks of their stay at those altitudes. Body composition changes have been inferred from the changes in body measurements, and soft tissue X-rays of the upper arm.

28. Bharadwaj H, AP Singh and MS Malhotra.
Body composition of the high-altitude natives of Ladakh: A comparison with sea-level residents.
Human Biology 45:423-434, 1973.

Authors' Abstract

Using anthropometric techniques, body composition was evaluated in three groups of young soldiers; 30 Tamilians at sea level, 45 Ladakhis at altitude and 17 Tamilians after a 10-month stay at 3960 m altitude, were studied. In the Tamilians at sea level, the body mass (mean 55.93 ±5.67 kg) was composed of 11.85 ±4.51% body fat, 5.52 ±0.62% bone mineral, 65.76 ±4.56% body water and 16.87 ±2.14% cell solids. Among Ladakhis (mean body weight 55.54 ±4.82 kg), fat constituted 10.58 ±2.73%, bone mineral 5.79 ±0.38%, body water 66.93 ±4.12% and cell solids 16.69 ±2.92% of the total body weight. Bone mineral was significantly greater in the Ladakhis due to their wider bi-iliac, wrist, knee and ankle widths. After 10 months' stay at high altitude, the Tamilians lost 0.89 kg body fat and 0.58 kg cell solids. Body water increased by 0.56 kg. Changes in bone mineral, however, were not significant.

In spite of prolonged exposure to high altitude, the Tamilians were unable to adjust the oxygen transport mechanism like the natives. Structural changes in the skeletal system of the high-altitude natives are obviously meant for better haemopoietic activity.

29. Bharadwaj H, MV Singh, SB Rawal, T Zachariah, S Kishnani, SN Pramanik, A Gupta and RM Rai.
Hydration and tissue solid content of the lean body on prolonged exposure to altitude.
*International Journal of Biometeorol*ogy 33:27-31, 1989.

Authors' Abstract

Using densitometric, hydrometric and anthropometric techniques, body fat, tissue solids, water and mineral content were quantitatively measured on two groups each of 26 young and healthy Indian soldiers of mixed ethnic composition. The experimental group was exposed to 3500 m altitude for 2 years and the experiments were carried out after 48 h and

3 weeks rehabilitation in Delhi (300 m). The control group was never exposed to high altitudes. In spite of the experimental group being fed with superior rations at high altitude, this group showed significantly hyperhydrated lean body with reduced tissue solids in comparison to the control group which was fed with identical rations in Delhi. The calculated mean density of the fat free body had declined to 0.092_10^3 kg/m^3. The 3 week stay at low altitude had little influence on body composition. Hyperhydration, with reduced tissue solids, would cause reduction in the density of fat free body, and would thus interfere with the estimates of total body fat based on densitometric procedures alone. In the hyperhydrated state, Siri's formula overestimated fat by 22.8% of the true value.

30. Bharadwaj H, KK Srivastava and MS Malhotra.
Body composition changes in the plains on descent from high altitude.
Human Biology 46:43-55, 1974.

Authors' Abstract

Body composition and serum metabolites were studied in 24 subjects at 4000 m and again after the first week and fourth week of rehabilitation in Delhi (216 m) when the level of physical activity and nutrition was considerably reduced. Significant gain in body weight was observed after one week of rehabilitation. This included significant gains in fat, cell solids and mineral content of the body. Body water, however, did not increase significantly. Gain in fat content was supported by significant increase in skinfold thickness during the first week. Skinfolds which are determinants of total body fat, continued to increase significantly throughout the rehabilitation period. Thickness of the skin folds at the extremities, however, tended to decline after the first week.

The increase in the cell solids after one week of rehabilitation was unexpectedly larger than the total increase in the lean body weight. The changes in the levels of serum alanine and aspartate amino-transferases as well as creatine phosphokinase indicate that the density of the lean body had increased owing to elevated protein synthesis and its retention in the intracellular spaces during this period. Increase in the density of the lean body without significant change in its volume would comply with experimental observations.

31. Bharadwaj H, SS Verma, T Zachariah, MR Bhatia, S Kishnani and MS Malhotra.
Estimation of body density and lean body weight from body measurements at high altitude.
European Journal of Applied Physiology 36:141-150, 1977.

Authors' Abstract

Body density and other anthropometric data were obtained on 101 Indian soldiers who were continuously staying at high altitude (3920 m) for more than 10 months. Use was made of a human body volumeter, and body density was calculated from observed body weight and volume. Measurements were taken on the body using standard techniques. A stepwise linear regression analysis was performed to establish possible relationships of 36 body measurements with density and lean body weight. Thigh anterior, juxta-nipple skin folds and forearm and ankle circumferences were selected in the regression equation predicting body density. Multiple correlation coefficient (R) equal to 0.765 was obtained for this equation. For the predicted lean body weight, R equaled 0.930. The regression equations included body weight, thigh anterior and juxta-nipple skin fold thicknesses, and forearm circumference. Contribution of other body measurements in the regression of these parameters was not significant. The analysis also revealed that a new set of coefficients is required for the measurements included in the published regression equations.

32. Bircher HP, U Eichenberger, M Maggiorini, O Oelz and P Bärtsch.
Relationship of mountain sickness to physical fitness and exercise intensity during ascent.
Journal of Wilderness Medicine 5:302-311, 1994.

Authors' Abstract

The purpose of the study was to investigate whether susceptibility to acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) is related to differences of physical fitness and/or the level of exercise during ascent. Work capacity at a heart rate of 170 min^{-1} (PWC_{170}) was assessed on a bicycle ergometer prior to high-altitude exposure, and the heart rate was continuously registered during the ascent from 3610 to 4559 m in 41 mountaineers. During the subsequent stay of 3 days at 4559 m, 12 subjects developed AMS, 13 subjects showed radiographic evidence of HAPE, and 16 subjects remained without significant illness. PWC_{170} (group means between 238 and 247 W) and heart rate during ascent (group means between 134 and 141 min^{-1}) did not significantly differ between these groups. PWC_{170} correlated negatively with two independent symptoms scores (clinical score, environmental symptom questionnaire) on day 3 at 4559 m, whereas heart rate during ascent correlated positively only with clinical score on days 2 and 3 at 4559 m. Correlations, however, were minor, with correlation coefficients of r = 0.32-0.43 (p<0.05-0.01). These results indicate that physical fitness or exercise intensity during ascent were of minor importance for the development of AMS and HAPE in our subjects.

33. Blume FD, SJ Boyer, LE Braverman, A Cohen, J Dirkse and JP Mordes.
Impaired osmoregulation at high altitude.
Journal of the American Medical Association 252:524-526, 1984.

Authors' Abstract

Osmoregulation was studied in 13 mountaineers who had experienced long-term exposure to high altitude on Mt. Everest. Serum osmolality rose from 290 ±1 mOsm/kg to 295 ±2 mOsm/kg at 5,400 m and finally to 302 ±4 mOsm/kg at 6,300 m after a mean of 26.5 days above 5,400 m. Despite this degree of osmoconcentration, plasma arginine-vasopressin concentration remained unchanged: 1.1 ±0.1 U/mL at sea level, 0.8 ± 0.1 U/mL at 5,400 m, and 0.9 ± U/mL at 6,300 m. Urinary vasopressin excretion was also similar at all three altitudes. We conclude that prolonged exposure to high altitude may result in persistent impairment of osmoregulation, caused in part by an inappropriate arginine-vasopressin response to hyperosmolality.

34. Bouissou P, CY Guezennec, FX Galen, G Defer, J Fiet and PC Pesquies.
Dissociated response of aldosterone from plasma renin activity during prolonged exercise under hypoxia.
Hormone and Metabolic Research 20:517-521, 1988.

Authors' Abstract

Six healthy male subjects on a fixed salt-diet performed 1 hour ergocycle exercise at 65% of $\dot{V}O_2$ max in normoxic (N) and hypoxic (H) conditions. Blood samples were taken at intervals for estimations of plasma aldosterone (PAC), angiotensin converting enzyme (ACE), adrenocortiotrophic hormone (ACTH) and catecholamine concentrations. Plasma volume reductions with exercise were similar in N (4.3 ±1%) and H (4.0 ±1%). PRA response to exercise was increased by hypoxia while PAC and plasma catecholamine rose to a similar extent in both conditions. Increases in ACTH concentration occurred at the end of exercise but no difference was found between high and low altitudes. Plasma ACE remained unchanged throughout exercise in either condition. These results indicate that hypoxemia interferes with PRA-mediated aldosterone secretion. The variations in plasma ACTH levels during exercise in hypoxia do not appear responsible for this interference.

35. Bouissou P, F Peronnet, G Brisson, R Helie and M Ledoux.
Fluid-electrolyte shift and renin-aldosterone responses to exercise under hypoxia.
Hormone and Metabolic Research 19:331-334, 1987.

Authors' Abstract

In order to describe fluid-electrolyte shift and endocrine response to exercise under moderate acute hypoxia, 8 healthy male subjects (24 ±3 years old) were evaluated at 40, 60, 80 and 100% $\dot{V}O_2$ max in normoxic (N) and hypoxic (H) conditions (14.5% O_2). $\dot{V}O_2$ max decreased from 55.5 ±1.3 to 45.8 ±1.4 ml/kg _ min in H condition. Plasma volume reductions with increasing relative

workloads were similar in N (9.4%) and H (9.9%) conditions. The rise in plasma osmolality was in part related to blood lactate accumulation which occurred in both conditions. However, variations in plasma solute content and osmolality suggested that exercise under hypoxia results in a greater electrolyte loss from vascular space and in a greater K^+ loss from working skeletal muscles. Increase in catecholamine concentrations were similar in normoxic and hypoxic conditions except for lower maximal norepinephrine concentration under hypoxia. Finally, although plasma renin activity increased with workload in both conditions, plasma aldosterone did not significantly change. This dissociation between renin and aldosterone suggests that aldosterone release during exercise might depend upon other factors. However, changes in plasma potassium concentration do not appear as an important stimulus for aldosterone secretion during exercise.

36. Boyer SJ and FD Blume.
Weight loss and changes in body composition at high altitude.
Journal of Applied Physiology 57:1580-1585, 1984.

Authors' Abstract

Little is known about weight loss and changes in body composition at extreme altitude. As part of the American Medical Research Expedition to Everest in 1981 we measured body weight, body fat, limb circumferences, dietary intake, 72-h stool fats, and 5-h urine xylose excretion at various altitudes on Caucasian and Sherpa expedition members. In Caucasians, loss of body fat accounted for 70.5% of the mean 1.9-kg weight loss during the approach march at moderate altitude, but for only 27.2% of the mean 4.0 kg weight loss during residence above 5,400 m. There was significant proportionate decrease in arm and leg circumferences during residence above 5,400 m (1.5 and 2.9 cm, respectively). On the other hand, Sherpas, who arrived in Base Camp with half as much body fat as Caucasian members (9.1% vs. 18.4%), maintained weight and limb circumferences during residence above 5,400 m. Fat absorption decreased 48.5% in three subjects, and xylose excretion decreased 24.3% in six of seven subjects at 6,300 m relative to sea level. It appears that muscle catabolism and malabsorption contribute significantly to weight loss at high altitude. High percent body fat does not protect against loss of muscle tissue. Sherpas do not appear susceptible to some of the changes affecting Caucasians.

37. Brahmachari HD, MS Malhotra, K Ramachandran and U Radhakrishnan.
Progressive changes in plasma cortisol, antidiuretic hormone and urinary volume of normal lowlanders during short stay at high altitude.
Indian Journal of Experimental Biology 11:454-455, 1973.

Authors' Abstract

Lowlanders taken to high altitude of 11,500 ft showed a rise in blood cortisol level within 3-9 days of arrival which returned to normal sea level in 13 days. Antidiuretic hormone showed a rise in 4 days and remained at a higher level despite the occurrence of diuresis in the subjects. Within 5 days of return to plains the plasma cortisol again showed a rise while the antidiuretic hormone reached normal level. Urine volume showed a rise with the antidiuretic at the same time, when the cortisol and ADH levels were highest. The cortisol response to hypoxic stress appears to be connected with the occurrence of acute mountain sickness.

38. Burrill MW, S Freeman and AC Ivy.
Sodium, potassium, and chloride excretion of human subjects exposed to a simulated altitude of eighteen thousand feet.
Journal of Biological Chemistry 157:297-302, 1945.

Authors' Abstract

Exposure to reduced pressure, under the conditions of the experiment, caused a temporary rise in the excretion of sodium, potassium, and chloride. Following exposure the excretion of these electrolytes was compensatorily reduced so that total excretion during the 24 hours was not altered. A temporary rise in urine volume was also found to accompany exposure.

It is possible that a reduced oxygen tension in the atmosphere may directly or indirectly influence the excretion of sodium and potassium in the urine; yet there is surprisingly little information on this subject in the literature. The possibility that the requirements for these elements might be altered in aviators or others maintained at high altitudes led to the study of this question in human subjects under conditions of simulated high altitude.

39. Buskirk ER and J Mendez.
Nutrition, environment and work performance with special reference to altitude.
Federation Proceedings 26:1760-1767, 1967.

Annotation

Purpose

This report deals with gross calorie and water requirements for resting and working man under environmental conditions of climate and altitude.

Methods

A brief graphic review was made of both old and more recent efforts to relate food and water requirements to variables associated with climate and physical work. Attention was paid only to the young man of average body build and stature who works in various environments.

Results

Studies during World War II indicated; as the environmental temperature decreases, that caloric intake increases, but considerations were given to variations in activity level. Studies undertaken in the late 1950's used the inclusion of body weight as a reference and the results showed that increasing physical activity clearly increased caloric intake in all environments. On the basis of studies in 1964, the evidence suggested that no more than a 2-5% increase in caloric allowance need be provided for adequately clothed persons in cold climates. If a caloric allowance adjustment is made for hot climates, it has been estimated that a 0.5% per degree centigrade increase is a sufficient adjustment for climates above 30^{0}C ambient temperature. After reviewing several investigations designed to evaluate caloric requirements at altitude, it was apparent that the interaction of many of the indirect effects of hypoxia usually served to stabilize caloric intake at levels comparable to those found at sea level for the man performing like amounts of work. In studies using well-condition track athletes, there was a 10% reduction in caloric intake with exposure to hypoxia, and this reduction was corrected within 3-4 days. Physical activity increases water requirements, particularly in warm and hot environments and at high altitude. About 13 mg of water vapor are lost for every liter of air expired if the vapor pressure gradient exceeds 20 mm Hg from the mouth and nose to ambient air. In a temperate environment when man is hypohydrated and subsequently exercises, his deep body temperature increases. This reaction reduces heat tolerance. As the body becomes hypohydrated, urine flow is reduced and the urine is maximally concentrated at about 1,400 milliosmols/liter with a daily urine volume of 500 ml or less.

*Conclusion*s

In the absence of abnormal climate situations and gross disturbances in thermal balance, the most important factor for determining caloric requirements is physical activity; for water requirements the important factors are environmental conditions including water vapor pressure plus physical activity.

40. Butterfield GE, J Gates, S Fleming, GA Brooks, JR Sutton and JT Reeves.
Increased energy intake minimizes weight loss in men at high altitude.
Journal of Applied Physiology 72:1741-1748, 1992.

Authors' Abstract

The hypothesis that high-altitude weight loss can be prevented by increasing energy intake to meet energy requirement was tested in seven men, 23.7 ±4.3 (SD) yr, taken to 4,300 m for 21 days. Energy intake required to maintain body weight at sea level was found to be 3,118 ±300 kcal/day, as confirmed by nitrogen balance. Basal metabolic rate (BMR), determined by indirect calorimetry, increased 27% on day 2 at altitude and then decreased and reached a plateau at 17% above the sea level BMR by day 10. Energy expended during strenuous activities was 37% lower at altitude than at sea level. Fecal excretion of energy, nitrogen, total fiber, and total volatile fatty acids as not significantly affected by altitude. Energy intake at altitude was adjusted after 1 wk, on the basis of the increased BMR, to 3,452 ±452 kcal/day. Mean nitrogen balance at altitude was negative (-0.25 ±0.71 g/day) before energy intake was adjusted but rose significantly thereafter (0.02 ±0.71 and 0.44 ±0.66 g/day during weeks 2 and 3). Mean body weight decreased 2.1 ±1.0 kg over the 3 wk of the study, but the rate of weight loss was significantly diminished after the increase in energy intake (201 ±75 vs. 72 ±48 g/day). Individual regression lines drawn through 7-day segments of body weight showed that in four of seven subjects the slopes of body weight were not significantly different from zero after the 2nd wk. Thus weight loss ceased in four of seven men in whom increased BMR at altitude was compensated with increased energy intake. This study demonstrates that weight loss at altitude can be minimized or even halted by increasing energy intake to meet increased energy need.

41. Carmena AO, N Garcia de Testa and FL Frias.
Urinary erythropoietin in men subjected to acute hypoxia.
Proceedings of the Society for Experimental Biology and Medicine 125:441-443, 1967.

Authors' Abstract

The urinary erythropoietin content of residents at sea level was measured during a 5-day sojourn at 14,900 feet. We found an early EP rise with the peak on the 2nd–3rd day of exposure. Thereafter, activity declined. The rapid increase in activity is considered to reflect the response to a severe hypoxic stimulus, and the subsequent decrease, to utilization of the hormone by an active erythroid bone marrow.

42. Chatterji JC, VC Ohri, KS Chadha, BK Das, M Akhtar, SC Tewari, P Bhattacharji and A Wadhwa.
Serum and urinary cation changes on acute induction to high altitude (3200 and 3771 metres).
Aviation, Space, and Environmental Medicine 53:576-579, 1982.

Authors' Abstract

Twenty subjects each were rapidly inducted by road to 3200 and 3771 m. Serum and urinary sodium, potassium, calcium, and magnesium were measured during 10 d at high altitude. At 3200 m, only serum potassium increased significantly on the 10th day. At 3,771 m serum potassium did not increase. Serum sodium generally remained low, serum magnesium increased, while calcium decreased significantly. Urinary volume over 24 h decreased more and for longer duration at 3771 m than at 3200 m. Urinary cations did not change significantly at 3200 m. At 3771 m, sodium and potassium excretion decreased on days 1 and 3 and later returned towards preinduction levels. Magnesium and calcium decreased throughout the high-altitude stay. Significant changes were noticed in serum and urinary cations on exposure to high altitude when adequate caloric intakes were not ensured.

43. Claybaugh JR, DP Brooks and A Cymerman.
Hormonal control of fluid and electrolyte balance at high altitude in normal subjects. *In: Hypoxia and Mountain Medicine. Proceedings of the 7th International Symposium,* edited by JR Sutton, G Coates, and CS Houston. New York: Pergamon Press, 1992. p.61-72.

Authors' Abstract

Ascent to high altitude results in imbalances of body fluids and electrolytes. The magnitude and direction of the imbalances are not consistent between studies because of the various schedules of ascent, severity and duration of hypoxia, prophylactic measures for prevention of high altitude sickness, and diet employed by investigators. Nonetheless, most studies indicate a loss in total body water. The body water is reduced as a consequence of increased insensible water loss, relatively constant urine output and a reduction in water intake resulting from decreased thirst. Thus, a transient negative water balance exists for the first 3-5 days at high altitude, resulting in a deficit of about 2 L in body water for up to 12 days. Decreased appetite also usually occurs upon ascent to high altitude, resulting in decrements of caloric intake of 1500 Kcal/day.

Consequently Na and K intakes are reduced, and increases in plasma renin activity and aldosterone concentration are observed several days after ascent. When appetite loss is less severe, renin levels are usually unchanged and aldosterone levels are reduced, reflecting what appears to be a more accurate response to hypoxemia per se. The antidiuretic hormone response to high altitude is complicated by an alteration in circadian rhythm. Most antidiuretic hormone responses at high altitude are probably indirect responses to the hypoxemia and the mechanisms are discussed.

44. Claybaugh JR, JE Hansen and DB Wozniak.

Response of antidiuretic hormone to acute exposure to mild and severe hypoxia in man.

Journal of Endocrinology 77:157-160, 1978.

Authors' Abstract

Eight men, 19-35 years of age, breathed 20.9% (normal oxygen), 13.9% (mild hypoxia) or 11.1% (severe hypoxia) oxygen in nitrogen gas mixtures during three 20 min periods, which were separated by 1 h recovery periods. The order in which the gas mixtures were breathed was random. The partial pressure of oxygen decreased from a mean of 93.5 during exposure to normal oxygen to 53.9 and 36.7 mmHg during mild and severe hypoxia, respectively. There were corresponding decreases in haemoglobin saturation. The partial pressure of carbon dioxide was lower and the pH higher during severe hypoxia than during exposure to normal oxygen. There were no changes in the plasma osmolality or in the concentrations of sodium or potassium in the plasma. There was a tendency for both the renin activity and the concentration of aldosterone in the plasma to decrease progressively as the percentage of oxygen breathed decreased. Unlike severe hypoxia, mild hypoxia suppressed the concentration of antidiuretic hormone (ADH) in the plasma of all subjects by about 59%; during severe hypoxia the reduction was not significant, being only about 33%. These data are consistent with the suggestion that the effect of hypoxia on the release of ADH is dependent on the level of hypoxia.

45. Claybaugh JR, CE Wade and SA Cucinell.

Fluid and electrolyte balance and hormonal response to the hypoxic environment.

In: Hormonal Regulation of Fluids and Electrolytes, edited by JR Claybaugh and CE Wade. New York: Plenum Press, 1989. p.187-214.

Authors' Abstract

High altitude exposure results in a negative water balance. This is in part due to increased insensible water loss, decreased thirst, an inappropriately maintained urine flow despite the decreased thirst, and a decreased appetite. The hormonal involvement in these responses is unclear. For instance, no clear cut role for any hormone system has been established for the decreased thirst. Similarly, the maintenance of urine flow despite decreased intake is not reflected in the short term by an alteration in the plasma osmolality to plasma ADH relationship. However, evidence after prolonged exposure suggests that the ADH response to increased osmolality is reduced. Also, increased cortisol and ANF levels may be contributing to the relative diuresis.

When dietary intake is controlled, high altitude is associated with a retention of potassium and a tendency to lose sodium. These responses are consistent with the reduced aldosterone levels which in turn are a result of a reduced responsiveness of aldosterone to renin. The mechanism of the latter is still unresolved.

The responses of ADH to hypoxia are very complex and have led to considerable confusion. We have tried to describe the differences in experimental designs that probably account for the reports of different responses. Clearly, degree of hypoxia, time of exposure, and whether or not the experiment allowed for spontaneous hyperventilation, are important considerations in comparing ADH responses from different studies.

The potential for hormonal involvement in acute mountain sickness, high altitude pulmonary edema, and cerebral edema continues as an important avenue of research aimed toward prevention and cure of these diseases. Lack of an animal model displaying these responses, and the present inability to use certain drugs in human studies has impaired progress. With eventual development of ANF antagonists, and approval to use ADH antagonists, more insight into these high altitude afflictions will be obtained.

46. Claybaugh JR, CE Wade, AK Sato, SA Cucinell, JC Lane and JT Maher.
Antidiuretic hormone responses to eucapnic and hypocapnic hypoxia in humans.
Journal of Applied Physiology 53:815-823, 1982.

Authors' Abstract

Urinary excretion rate of antidiuretic hormone ($U_{ADH}\dot{V}$) was studied in male volunteers in response to hypobaric hypoxia. The first series consisted of three groups. The chamber was decompressed to 465, 495, and 438 Torr during high-altitude (HA) exposure for groups I (n = 5), II (n = 5) and III (n = 4), respectively. In group I, the chamber air contained 3.77% CO_2 to prevent alkalosis. The level of hypoxemia was similar in groups I and II. Mean 24-h U_{ADH} was unchanged in group I, but increased 96% (P<0.05) and 180% (P<0.05) in groups II and III, respectively, on day 1 at HA and was normal during subsequent days at HA regardless of symptoms of acute mountain sickness. Shorter sampling intervals employed in a second series of experiments conducted at 495 Torr revealed a twofold increase in $U_{ADH}\dot{V}$ (P<0.05) 8-12 h after ascent in eight asymptomatic subjects; $U_{ADH}\dot{V}$ returned to base line within 9 h and remained low. The symptomatic subjects both had increased $U_{ADH}\dot{V}$ (3- and 8-fold from base line) between 2 and 4 h after ascent. Increased $U_{ADH}\dot{V}$ in asymptomatic subjects may be a result of the concomitant decrease in plasma volume, both of which appeared to be eliminated by CO_2 supplementation.

47. Colice GL and G Ramirez.
Effect of hypoxemia on the renin-angiotensin-aldosterone system in humans.
Journal of Applied Physiology 58:724-730, 1985.

Authors' Abstract

Hypoxemia was induced in five subjects older than 40 (group 1) and five younger than 35 yr (group 2) on normal and low-salt diets by having the subjects breathe hypoxic gas. The fractional inspired O_2 of the hypoxic gas was regulated so that group 1 hemoglobin saturations fell to 90% for 1 h. Group 2 subjects had desaturation to 90% for 1 h followed by desaturation to 80% for a 2nd h. Plasma renin activity (PRA), angiotensin-converting enzyme activity (ACE), and plasma cortisol levels did not change during hypoxemia. Plasma aldosterone levels fell in both groups during the 1st h of hypoxemia. Decreases were greatest during salt restriction and were significant (P<0.01) for the combined groups. Plasma aldosterone levels plateaued during the 2nd h of more severe hypoxemia in group 2. Hepatic blood flow, measured by indocyanine green clearance, and the adrenal response to exogenous adrenocorticotropic hormone, measured by changes in plasma cortisol and aldosterone, were not changed by hypoxemia in group 2 subjects. These results indicate that plasma aldosterone falls during hypoxemia despite unchanged PRA, ACE, hepatic blood flow, and adrenal function.

48. Colice GL and G Ramirez.
Aldosterone response to angiotensin II during hypoxemia.
Journal of Applied Physiology 61:150-154, 1986.

Authors' Abstract

Exercise in humans causes increases in plasma renin activity (PRA) and plasma aldosterone concentrations (PAC) except when performed at high altitude or while the subjects breathe hypoxic gas. Under those conditions, PRA increases with exercise but PAC does not. We speculated that the PAC suppression during hypoxemic exercise was due to hypoxemia-induced release of a circulating inhibitor of angiotensin II-mediated aldosterone secretion. To test this hypothesis, we measured the PAC response to graded infusions of angiotensin II during hypoxemia and normoxemia. Eight normal volunteers were given increasing doses of angiotensin II (first 2 $ng \cdot kg^{-1} \cdot min^{-1}$ and then 4, 8, and finally 12 $ng \cdot kg^{-1} \cdot min^{-1}$, each for 20-min periods) on 2 separate days, once while breathing room air and the other day while breathing hypoxic gas adjusted to maintain the subjects' hemoglobin saturation at 90%. The PAC response to different doses of angiotensin II did not significantly differ during

hypoxemia from normoxemia. We conclude that our model of hypoxemia does not cause release of an inhibitor of angiotesin II-mediated aldosterone release.

49. Consolazio CF, LO Matoush, H Johnson and TA Daws.
Energy, nitrogen, and water requirements on normal adults residing at 4,300 m for 28 days.
Denver, CO: Fitzsimons General Hospital.
U.S. Army Medical Research and Nutritional Laboratory Report No.308, July, 1967. 22p.

Authors' Abstract

Balance studies were conducted on three groups of young, healthy adults between the ages of 18-24 years. After control studies, Group I was taken to 4,300 meters gradually, Group II was taken to 4300 meters abruptly, and Group III remained at sea level during the entire study. One-half of each group was physically conditioned. No significant differences were observed in nitrogen, and fluid balances between (a) the groups that were taken to altitude gradually or abruptly, or (b) between the groups that were physically conditioned, and those who did not exercise. As a result, the respective groups were combined for comparative purposes.

Three factors were prominent during the 28-day high altitude exposure to 4300 meters that included (a) a decrease in food intake which is probably due to anorexia caused by the clinical symptoms, (b) a negative nitrogen balance which may be due to the decreased nutrient intake and the increased requirement for energy, and (c) a negative fluid balance due to involuntary dehydration and other undetermined factors. These factors appeared to be somewhat less in Group I who ascended to altitude gradually, and suggests the beneficial effects of ascending to high altitude gradually.

These and other related problems require considerable investigation in the near future.

50. Consolazio CF, HL Johnson and HJ Krzywicki.
Body fluids, body composition, and metabolic aspects of high-altitude adaptation.
In: Physiological Adaptations-Desert and Mountain, edited by MK Yousef, SM Horvath and RW Bullard. New York: Academic Press. Chap. 16, 1972. p.227-241.

Authors' Abstract

Anorexia accompanied by body weight losses and negative water and nitrogen balances were observed in the 1964 and 1967 studies. In the 1967 and 1968 studies, AMS was drastically reduced. The daily caloric consumption in human subjects can be maintained after abrupt exposure to high altitude, providing the men have reduced severity of AMS and are in good physical condition prior to and during altitude exposure. This study indicates that (a) positive nitrogen balances can be achieved during altitude exposure; (b) body weight losses can be greatly reduced; (c) mineral balances are positive; (d) blood electrolyte levels are normal; and (e) fasting glucose levels and glucose tolerance curves are normal. Normal digestion and absorption occurred during acute altitude exposure. It appears that many of the biochemical changes that occur during abrupt high altitude exposure, previously attributed to hypoxia, may be the result of anorexia and the subsequent caloric restriction.

Since total body water and intracellular water are significantly decreased during acute altitude exposure, it appears that hypohydration and a natural diuresis occurs. This appears to be an adaptive mechanism that may reduce cerebrospinal pressure, and cerebral edema, the presence of which reduces the severity of AMS. The severity of AMS during abrupt altitude exposure can be greatly reduced without the use of drug therapy. The following conditions appear to be highly beneficial; (a) heavy physical activity and physical conditioning prior to altitude exposure; (b) the consumption of a minimal quantity of carbohydrate (at least 320 gm/day), (c) the maintenance of a normal food intake at altitude, and (d) a natural "cold" diuresis, with a subsequent decrease in total body water and intracellular water.

51. Consolazio CF, LO Matoush, HL Johnson and TA Daws.
Protein and water balances of young adults during prolonged exposure to high altitude (4,300 meters).
The American Journal of Clinical Nutrition 21:154-161, 1968.

Authors' Abstract

Balance studies were conducted on three groups of young healthy adults between the ages of 18 and 24. After control studies, group 1 was taken to 4,300 m gradually, group 2 was taken to 4,300 m abruptly, and group 3 remained at sea level during the entire study. One-half of each group was physically conditioned. No significant differences were observed in nitrogen and fluid balances between a) the groups that were taken to altitude gradually or abruptly, or b) between the subgroups that were physically conditioned and those who did not exercise. The exercisers and nonexercisers in each group were combined for statistical comparisons.

The two factors which were prominent during the 28-day high-altitude exposure to 4,300 m by groups 1 and 2 were a) negative nitrogen balances which may have been due to the decreased utilization of protein and the increased requirement for energy, the possible decrease in protein synthesis at altitude, or a combination of these; and b) negative fluid balances due to involuntary dehydration and other undetermined factors. The negative nitrogen balance appeared to be somewhat less in group 1, which ascended to altitude gradually, and this suggests the beneficial effects of ascending gradually to high altitude. Group 3, which remained at sea level during the entire study, was in nitrogen and fluid balance during the entire study.

52. Cosby RL, AM Sophocles, JA Durr, CL Perrinjaquet, B Yee and RW Schrier.
Elevated plasma atrial natriuretic factor and vasopressin in high altitude pulmonary edema.
Annals of Internal Medicine 109:796-799, 1988.

Authors' Abstract

A diagnosis of acute high-altitude pulmonary edema was made in five male skiers (age, 35.0 ±1.8 years) by history and physical examination and was confirmed by a characteristic chest radiogram showing alveolar infiltrates associated with a normal cardiac silhouette. Five healthy age- and sex-matched subjects with similar physical activity at the same altitude served as controls. Plasma sodium was 135.0 ±1.5 mmol/L in the acutely ill patients compared with 144.0 ±3.3 mmol/L in the controls ($P<0.025$). Mean plasma atrial natriuretic factor immunoreactivity averaged 17.6 ±5.6 pmol/L in patients with high-altitude pulmonary edema compared with 6.8 ±0.7 pmol/L in the controls at the same altitude ($P<0.05$). Elevated atrial natriuretic factor levels normalized to 7.5 ±1.9 pmol/L ($P<0.05$) during recovery in Denver (altitude, 1600 meters) 24 hours later. Plasma arginine vasopressin levels were 1.8 ±0.37 pmol/L in patients with high-altitude pulmonary edema at diagnosis compared with 0.92 ±0.28 pmol/L in controls ($P=0.07$). The inappropriately elevated arginine vasopressin levels decreased to 1.29 ±0.37 pmol/L during recovery ($P<0.025$), but the lowered plasma sodium concentration had not normalized by discharge within 24-hours of transfer to Denver and averaged 135.8 ±1.2 mmol/L. The pathophysiologic implications of these findings are discussed.

53. Cunningham WL, EJ Becker and F Kreuzer.
Catecholamines in plasma and urine at high altitude.
Journal of Applied Physiology 20:607-610, 1965.

Authors' Abstract

The concentration of free epinephrine and norepinephrine in plasma and 24-hr urine samples, collected from members of the Dutch Monte Rosa expedition (July 1963) was investigated during 17 days at various altitudes up to 4,560 m. The results indicate that the levels of both plasma and urine catecholamines were elevated during the expedition, the plasma levels reaching a maximum towards the end of the 12 days sojourn at 4,560 m. In general there was a twofold increase in total catecholamine concentration in the samples collected at high altitude as compared to control values at sea level. This difference was due to a significant increase in the norepinephrine concentration; there was little change in epinephrine level.

54. Delamare JP.

Birmingham Medical Research Expeditionary Society 1977 Expedition: Changes in renal function observed during a trek to high altitude. *Postgraduate Medical Journal* 55:487-491, 1979.

Authors' Abstract

Changes in renal function were observed in 17 subjects during the course of a trek to high altitude. Comparison was made between these changes and the clinical assessment of acute mountain sickness (AMS).

Periods of natriuresis occurred during ascent and descent, that during ascent being related to a fall in plasma aldosterone. Alterations in serum and urinary potassium suggested that potassium retention occurred during the ascent to altitude.

No significant correlation occurred between changes in renal function and the severity of AMS before the illness being clinically apparent. When this was so, the severity of AMS correlated with a decreasing urine output, increasing positive fluid balance and a decreasing excretion of sodium and potassium; these changes were produced in part by a decrease in glomerular filtration rate.

55. Dill DB, K Braithwaite, WC Adams and EM Bernauer.

Blood volume of middle-distance runners: effect of 2,300-m altitude and comparison with non-athletes. *Medicine and Science in Sports and Exercise* 6:1-7, 1974.

Authors' Abstract

Concurrent with the study of performance and aerobic power of 12 highly trained, superior middle-distance runners before, during and after 3 weeks of strenuous training at 2,300-m altitude, observations were made pre- and post-altitude on blood volume, BV, plasma volume, PV, cell volume, CV, hematocrit, Hct_v, and the concentration and amount of hemoglobin, Hb. For comparative purposes, the same componenets were measured in 21 non-athletic young men at or near sea level. Similar data on 27 black and white sharecroppers also were available for comparison. Since CV did not change at altitude, Hct_v values obtained on eight occasions at altitude were used to calculate PV at altitude. The mean Hct_v increased 3.7% at altitude, which corresponds to a decrease of 6.6% in PV. The mean decrease in body weight, BW, was 21. In the runners BV in relation to BW was 21% greater than in 48 non-athletes. Approximately one-third of this larger BV is accounted for by the lower body fat of the runners. Cell volume, PV and total Hb, all in relation to BW, were greater in the runners than in the non-athletes by 18, 24, and 16%, respectively. Consistent with the difference in PV and in CV, Hb concentration was 4% lower in the runners. It is concluded that endurance athletes have thin blood, but so much of it that their total Hb exceeds that of non-athletes. Aerobic power was dependent in part on Hb/kg not only in the runners but also in girl swimmers.

56. Dill DB, FG Hall, KD Hall, C Dawson and JL Newton.

Blood, plasma, and red cell volumes: age, exercise, and environment. *Journal of Applied Physiology* 21:597-602, 1966.

Authors' Abstract

Observations have been made on blood components of seven men in the hot desert and on two of them at 3,800 m 1 week after leaving the desert. Similar observations made in the desert on Dill 32 years before are recorded. No notable change occurred in blood components at rest during the first days in the desert; even in a bout of exercise there generally were no changes. In two men who engaged in frequent strenuous exercise during a 5-week period, their was a decline in total red cell volume and an increase in plasma volume with no change in blood volume. These two men, Phillips age 34 and Dill age 73, then made the transition to the Barcroft laboratory with a decrease in barometric pressure from 694 to 485 mm Hg and in maximum temperature from above 40 to about 15 C. Phillips showed an increase in hemoglobin concentration and a decrease in plasma volume. Dill had a decrease in hemoglobin concentration and an increase in plasma volume. In the light of this and other evidence it appears that the response of plasma volume in the first days at high altitude is to

decline in youth and to increase in age. From age 41 to age 73, Dill's plasma volume has decreased about one-sixth and red cell volume about 6%.

57. Dill DB, SM Horvath, TE Dahms, RE Parker and JR Lynch.
Hemoconcentration at altitude.
Journal of Applied Physiology 27:514-518, 1969.

Authors' Abstract

Concentration of hemoglobin in blood ($(Hb)_b$), blood volume (BV), and related observations were made on 12 men, aged 18 to 77 years, during 2-6 weeks at 3,800 m. Concentration of hemoglobin in red cells ($(Hb)_c$) and red cell volume (CV) remained constant at altitude although in some men CV increased postaltitude. With $(Hb)_c$ and CV constant, plasma volume (PV) could be calculated from $(Hb)_b$. Mean $(Hb)_b$ increased 17% in 2 weeks; PV decreased. However, in Dill, aged 77 years, during the first week $(Hb)_b$ decreased and PV increased and in ERN, aged 26 years, $(Hb)_b$ was nearly unchanged for 8 days. Neither increases nor decreased in $(Hb)_b$ correlated with changes in body weight which presumably reflected changes in body water. While concentration of plasma protein $(P)_s$ generally increased in the first weeks at altitude, total plasma protein did not change consistently. Within 24 hr postaltitude $(Hb)_b$, PV, and $(P)_s$ returned to, or nearly to, prealtitude values.

58. Dill DB, JH Talbott and WV Consolazio.
Blood as a physicochemical system. XII. Man at high altitudes.
Journal of Biological Chemistry 118:649-666, 1937.

Authors' Abstract

The distribution of combined CO_2 between arterial cells and serum is unchanged at high altitudes aside from the responses due to changes in pH and per cent saturation with oxygen. There appears to be a decreased proportion of chloride in cells (Fig. 1). Owing to increase in the proportion of red cells, the buffer value of blood is increased; the pH, change in the respiratory cycle is one-fourth less. At the same time the decreased alkaline reserve reduces the capacity of the body to neutralize fixed acids. The increase in hemoglobin and decrease in alkaline reserve occur slowly; months may be required for hemoglobin to reach a maximum and arterial CO_2 content, a minimum.

The electrolytes of serum at high altitude were found to undergo one major change, whether measured in milli-equivalents or in per cent of the sea-level value. This is the decrease in bicarbonate. At 5.34 km. this may be 8 milli-equivalents, while the Cl increase is 4 milli-equivalents and the Na decrease, 2 milli-equivalents, leaving an unexplained anion deficit of about 2 milli-equivalents. Other ions are remarkable for their stability.

A synthetic description is given of the blood of fully adapted workmen living at 5.34 km. and working at 5.80 km.

59. Durkot MJ, RW Hoyt, A Darrigrand, LJ Hubbard, GH Kamimori and A Cymerman.
Chronic hypobaric hypoxia decreases intracellular and total body water in microswine.
Comparative Biochemistry and Physiology 114A:117-121, 1996.

Authors' Abstract

The effects of hypobaric hypoxia on body fluid distribution were studied in five unanesthetized immature microswine (body weight 17.1 ±1.5 kg, mean ±SEM) at sea level and after 23 days of simulated altitude exposure (427 Torr, 4600 m, 24^{0}C, 50% RH). Total body water (TBW), extracellular fluid volume (ECF), and plasma volume (PV) were determined with D_2O, NaBr, and indocyanine green, respectively. Intracellular fluid volume (ICF = TBW - ECF) and interstitial fluid volume (ISF = ECF - PV) were calculated. Hypoxia resulted in characteristic decreases ($P<0.05$) in arterial PO_2 and PCO_2, and an increase in hemoglobin concentration. Chronic exposure to hypobaric hypoxia elicited significant ($P<0.05$) decrements in body weight gain (-14%), TBW (-11%, 12.5 vs 11.3 L), ICF volume (-13%, 8.9 vs. 7.8 L) and PV (-28%, 0.82 vs. 0.57 L). Although the ECF was unaffected (3.66 vs. 3.57 L), the ISF was significantly increased (+6%, 2.83 vs. 3.22 L) ($P<0.05$). Decreased TBW accounted for 51% of the expected reduction in body mass. These results suggest that the

suppression in body weight gain is partially accounted for by decreases in TBW, ICF, and PV. In addition, the apparent elevation of ISF occurring concurrently with decreases in ICF and PV may be related to the development of edema, which can accompany exposure to high altitude.

60. du Souich P, C Saunier, D Hartemann, A Sautegeau, H Ong, P Larose and R Babini.
Effect of moderate hypoxemia on atrial natriuretic factor and arginine vasopressin in normal man.
Biochemical and Biophysical Research Communications 148:906-912, 1987.

Authors' Abstract

The object of this study was to assess the effect of moderate acute hypoxemia on plasma concentrations of atrial natriuretic factor (ANF), arginine vasopressin (AVP), plasma renin activity (PRA) and urinary excretion of prostaglandin E_2 ($U_{PGE2}\dot{V}$). Eight volunteers were exposed for 2 hours to a gas mixture containing 10% O_2, 4.5% CO_2 and 85.5% N_2. Hypoxia increased diastolic blood pressure and free water clearance. Hypoxia did not change the AVP, PRA, or $U_{PGE2}\dot{V}$, although increased ANF from 17.7 ±3.4 pg/ml to 27.2 ±1.7 pg/ml ($p<0.005$) at 120 minutes. ANF changes were closely associated with the rise in blood pressure.

61. Eckardt K-U, U Boutellier, A Kurtz, M Schopen, EA Koller and C Bauer.
Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia.
Journal of Applied Physiology 66:1785-1788, 1989.

Authors' Abstract

This study was carried out to investigate the early changes in erythropoietin (EPO) formation in humans in response to hypoxia. Six volunteers were exposed to simulated altitudes of 3,000 and 4,000 m in a decompression chamber for 5.5 h. EPO was measured by radioimmunoassay in serum samples withdrawn every 30 min during altitude exposure and also in two subjects after termination of hypoxia (4,000 m). EPO levels during hypoxia were significantly elevated after 114 and 84 min (3,000 and 4,000 m), rising thereafter continuously for the period investigated. Mean values increased from 16.0 to 22.5 mU/ml (3,000 m) and from 16.7 to 28.0 mU/ml (4,000 m). This rise in EPO levels corresponds to 1.8-fold (3,000 m) and 3.0-fold (4,000 m) increases in the calculated production rate of the hormone. After termination of hypoxia, EPO levels continued to rise for 1.5 h and after 3 h declined exponentially with an average half-life time of 5.2 h.

62. Eckardt K-U, J Dittmer, R Neumann, C Bauer and A Kurtz.
Decline of erythropoietin formation at continuous hypoxia is not due to feedback inhibition.
American Journal of Physiology 258:F1432-F1437, 1990.

Authors' Abstract

Serum erythropoietin (EPO) levels in response to hypoxia are known to decline before an increase in blood oxygen carrying capacity. To define the possible mechanisms underlying this phenomenon, we have investigated 1) how renal EPO mRNA content and EPO production rate underlying the early kinetics of serum EPO levels change under different degrees of normobaric hypoxia, and 2) if a feedback inhibition of either EPO formation or EPO survival in the circulation exists by the hormone itself. We found that serum immunoreactive EPO levels in rats peaked after 12-h exposure to 7.5 or 9% oxygen (2,949 ±600 and 756 ±108 mU/ml, respectively, mean ±SE) and declined to 29 and 64% of peak levels, respectively, after 36 h of hypoxia. EPO levels in response to 11.5% oxygen showed no consistent change between 12 (122 ±21 mU/ml, mean ±SE) and 36 h (182 ±35 mU/ml) of hypoxia. The decline in EPO levels under severe hypoxia (7.5% O_2) was paralleled by a marked reduction in renal EPO mRNA content, indicating that it was primarily a result of diminished hormone production. The observed reductions in serum EPO after 36 h corresponded to preceding declines of calculated EPO production rates from 163- to 62-fold (7.5% O_2) and 36- to 25-fold (9% O_2) basal values. Application of 50 IU recombinant human EPO to rats 12 h, 6 h, or

immediately before hypoxic exposure to mimic the early increase in EPO levels did not affect endogenous EPO formation during a subsequent hypoxic exposure of 12 h. These results indicate that the early decrease in EPO production at continuous hypoxia is not mediated by a negative feedback control through the effect of EPO on its production sites or target cells. Although the reduction in EPO production rate occurs independent of the amount of EPO produced, the magnitude of the decline appears to be related to the degree of the preceding stimulation.

63. Epstein M and T Saruta.
Effects of simulated high altitude on renin-aldosterone and Na homeostasis in normal man.
Journal of Applied Physiology 33:204-210, 1972.

Authors' Abstract

The effects of chronic exposure to an environment of a reduced barometric pressure (258 mm Hg) without concomitant hypoxia (hypobaria) on plasma renin activity (PRA), urinary aldosterone excretion (AER), and sodium, potassium, and fluid homeostasis were assessed in eight normal male subjects. Following dietary sodium restriction, sodium balance was attained more rapidly during hypobaria than during control (Na $t_{1/2} = 0.57$ vs 0.70 days) ($P<0.05$) with a smaller decrement in body weight (-1.1% vs -2.6%) ($P<0.001$). Creatinine clearance decreased progressively throughout hypobaria, with the decrease approximating 40% by day 8. Renin-aldosterone responsiveness following dietary sodium restriction was unimpaired during hypobaria. These data suggest that hypobaria alters sodium homeostasis by establishing a new steady state of sodium balance which may be mediated in part by a decrease in the filtered load of sodium.

64. Epstein M and T Saruta.
Effects of an hyperoxic hypobaric environment on renin-aldosterone in normal man.
Journal of Applied Physiology 34:49-52, 1973.

Authors' Abstract

The effects of chronic exposure to a simulated spacecraft environment of 100% oxygen at reduced total barometric pressure (258 mmHg) (hyperoxia) on plasma renin activity (PRA), urinary aldosterone excretion (AER), and sodium homeostasis were assessed in eight normal male subjects. Renal sodium conservation during hyperoxia, as assessed by days to balance following dietary sodium restriction, was similar to control (3.4 ±0.3 vs. 3.1 ±0.2 days) ($P>0.05$). Renin-aldostersone responsiveness following dietary sodium restriction during hyperoxia did not differ from control. These data suggest that the decrease in AER during high-altitude exposure is attributable to a decrease in partial pressure of oxygen rather than a reduction in barometric pressure per se and that the hyperoxic hypobaric atmosphere currently utilized in manned space flight does not contribute to the disturbance in sodium and fluid homeostasis regularly observed during manned orbital missions.

65. Farber MO, M Heyes, D Robertshaw, G Robertson and M Weinberger.
Renal and endocrine responses to hypoxia and hypobaria.
Clinical Research 28:720A, 1980. (Abstract)

Authors' Abstract

The effect(s) of hypoxia on renal and endocrine function in man have remained ill-defined. 4 groups of normal subjects were studied under conditions of H_2O diuresis. Gp I (controls) n = 5; Gp II (Hypoxic Hypobaria, barometric pressure (P_B = 400 Torr) n = 14; Gp III (Hypoxic Normobaria, 10.5% O_2) n = 4; Gp IV (Normoxic Hypobaria, P_B = 400 Torr, 40% O_2) n = 4. Experimental exposures were 1 hour. Parameters monitored included: urine volume (U_V), osmolality, sodium; plasma arginine vasopressin (AVP), cortisol (Cort), renin, aldosterone, prolactin (Prl), osmolality, sodium; blood pressure (MAP); blood gases. Group II showed 2 distinct responses: A, maintained diuresis and slight drop in MAP; B, marked antidiuresis and much greater drop in MAP. Pertinent data (hypoxic values, % of respective controls);

	U_V	Uosm	AVP	Cort	Prl	MAP
IIA n=7	108	97	83	98	131*	90*
IIB n=7	38*	251*	22044*	220*	236*	82*

*p<0.05

There was a positive correlation between fall in MAP and AVP increase. Highest AVP's (>5000%, n = 2) were associated with nausea, but significant elevations were observed in the remaining non-nauseated subjects. In Group III 2/4, with the greatest fall in MAP, responded similarly to IIB subjects but Prl did not increase in any. Group IV subjects responded as controls. These data suggest: 1) antidiuresis during hypoxia may be mediated through AVP stimulation caused by either nausea or large falls in MAP; 2) hypoxic hypobaria is a more potent stimulus of Prl release than a comparable level of hypoxic normobaria; 3) increases in Prl during hypoxia exert no measurable effect on H_2O diuresis.

66. Faura J, J Ramos, C Reynafarje, E English, P Finne and CA Finch.
Effect of altitude on erythropoiesis.
Blood 33:668-676, 1969.

Authors' Abstract

Measurements were made to characterize the relationship between erythropoietin output and erythropoiesis in two groups of subjects, one moved from a sea level habitat to high altitude, and the second moved from a high altitude habitat to sea level. In the first group, there was a latent period of 6 hours followed by a rapid increase in erythropoietin, and a secondary fall to a level of approximately twice normal. The increased erythropoietin stimulus was also reflected in a shortened marrow radioiron transit time. In the second group, there was an initial unexplained rise, after which erythropoietin fell within 8 hours to undetectable amounts.

Elevated erythropoietin was associated in Group I with an increased iron uptake within 24 hours of the stimulus, suggesting a direct action of erythropoietin on hemoglobin synthesis by the existing marrow population. Limitation in erythropoiesis to a rate of less than twice normal was tentatively explained by a restricted iron supply. In the second group, marrow activity continued for 3 days despite a marked fall in erythropoietin, indicating that cells in the maturation phase completed their normal development.

67. Fenn CE.
Energy and nutrient intakes during high-altitude acclimatization.
Journal of Wilderness Medicine 5:318-324, 1994.

Author's Abstract

Information on the food intake of free living individuals during the initial stage of an expedition, when the diet is based on fresh and locally available foods, is scarce. A weighed dietary survey was carried out by 10 healthy unacclimatized male subjects who walked from an altitude of 2430 m to Everest Base Camp (5400 m) in 10 days. All food and fluids consumed during the study period were weighed using dietary scales and recorded in food record books. The mean daily energy intake was 10.03 (SE 1.26) MJ. The average body weight loss was 2.07 (SE 0.6) kg and there was no change in percentage body fat calculated from skinfold thickness measurements. The percentage energy from carbohydrates in the diet was significantly higher ($p<0.05$) in the final 3 days (59%, SE 2.0) compared with the first 3 days of the study period (51%, SE 3.6). It is likely that the high carbohydrate intake reflected the availability of foods at this time. With the exception of folic acid and vitamin C, the mean daily intakes of B vitamins, iron, and zinc exceeded the UK Dietary Reference Values. However, these values refer to healthy populations but not to those exposed to high altitude when nutrient requirements may be increased.

68. Fletcher RF.
Birmingham Medical Research Expeditionary Society 1977 expedition: Signs and symptoms.
Postgraduate Medical Journal 55:461-463, 1979.

Author's Abstract

The BMRES group of 17 persons is described and details are given of the trek to 5400 m. The research programme is outlined. Moderately severe acute mountain sickness (AMS) was observed in 5 subjects. All subjects were rated according to their symptoms related to AMS by interview, peer review and self-assessment, and the results compared.

69. Forsling ML and JS Milledge.
Effect of hypoxia on vasopressin release in man.
Journal of Physiology (London) 267:22-23, 1977.

Annotation

Purpose

To observe vasopressin release during laboratory induced hypoxia and to investigate hypoxia induced oliguria leading to pulmonary oedema.

Methods

Five male subjects known to acclimatize well at high altitude were observed during delivery of 10.0-10.5% O_2 via RAF mask. Subjects were observed at baseline and after 4 hr of O_2 delivery. Blood samples were collected via a catheter at hourly intervals and at 3, 9, and 27 min after staring hypoxia (urine was passed every 20 min). Subjects were returned to air breathing via the RAF mask for 90 min.

Results

Little change was observed in vasopressin release during hypoxia (0.1 ±0.15 U/ml, n = 26) compared to the baseline (0.7 ±0.17 U/ml S.E.M., n = 10). Urine flow was maintained during hypoxia with the ratio of urine to plasma osmolarity remaining above one for only two subjects. Plasma pH showed no significant change and urinary pH increased by 0.18 ±0.06 (n = 4) during the experimental period.

Conclusion

For subjects who acclimatize well at high altitude, hypoxia has little effect on vasopressin release.

70. Frayser R, ID Rennie, GW Gray and CS Houston.
Hormonal and electrolyte response to exposure to 17,500 ft.
Journal of Applied Physiology 38:636-642, 1975.

Authors' Abstract

Hormone, electrolyte, and body fluid compartment changes were studied in subjects who either spent time at 10,000 ft before flying to 17,500 ft, or were premedicated with acetazolamide and flown directly to 17,500 ft. In the former group at 10,000 ft, renin and aldosterone were not different from control. Cortisol increased significantly from 9.8 to 19.5 g/100 ml on the third day. At 17,500 ft renin, aldosterone and cortisol were significantly elevated on day 3 but had returned to control levels by day 5. Sodium and potassium excretion was significantly reduced at both altitudes. Total body water, extracellular and plasma volumes were reduced (P<0.05) at 17,500 ft. Subjects pretreated with acetazolamide and flown directly to 17,500 ft had significant increases (P<0.001) in plasma renin, aldosterone, and cortisol levels during the first 4 days at altitude. On day 1 there was a decrease of 45% in sodium and 38% in potassium excretion. One day 4 there was a decrease of 63% and 51%, respectively. These changes are not associated with the premedication. The initial changes may reflect the immediate response to stress and alkalosis followed by a return to control levels as the body adapts to altitude.

71. Fulco CS, A Cymerman, NA Pimental, AJ Young and JT Maher.
Anthropometric changes at high altitude.
Aviation, Space, and Environmental Medicine 56:220-224, 1985.

Authors' Abstract

Eight white males (18-25 yr) were evaluated before, during and after 18-d residence on the summit of Pikes Peak, CO (4300 m; high altitude, HA) to describe the anthropometric changes associated with weight loss and to test the accuracy of a number of previously published prediction equations in assessing any alteration of the relative fat-to-lean tissue ratio during exposure to HA. Body weight (BW), 10 circumference (C), and 7 skinfold (SF) measurements were obtained preprandial at sea level (SL) and on days 2,4,6,9,12,16 and 18 at HA. Body density was estimated by hydrostatic weighing (HW) pre- and post-HA. BW differed from SL (p<0.01) after day 9 at HA. HW indicated that the pre- to post-HA weight loss was partitioned into a 2.06 kg loss in fat-free body mass (p<0.001) and an insignificant increase in fat wt (0.58 kg). Percent body fat (BF) increased from 16.6 to 17.7 (p<0.02). After day 9 of HA, the sum of SF and C measurements increased (p<0.02) and decreased (p<0.05) from SL, respectively. The largest changes occurred in the chest and scapula SF and in the

C of the hip, neck, calf, and two abdominal sites. The alterations in triceps, waist, and total SF were related to the increase in fat weight and BF (r >0.71). The decrements in C were related only to the loss in BW (r >0.83). Based on the lack of concurrence with the results from the hydrostatic weighings, it was concluded that SF and C measurements and/or prediction equations do not provide an accurate assessment of the altered fat-to-lean ratio during weight loss at high altitude.

72. Fulco CS, RW Hoyt, CJ Baker-Fulco, J Gonzalez and A Cymerman.
Use of bioelectrical impedance to assess body composition changes at high altitude.
Journal of Applied Physiology 72:2181-2187, 1992.

Authors' Abstract

This study determined the feasibility of using bioelectrical impedance analysis (BIA) to assess body composition alterations associated with body weight (BW) loss at high altitude. The BIA method was also evaluated relative to anthropometric assessments. Height, BW, BIA, skinfold (SF, 6 sites), and circumference (CIR, 5 sites) measurements were obtained from 16 males (23-35 yr) before, during, and after 16 days of residence at 3,700-4,300 m. Hydrostatic weighings (HW) were performed pre- and post-altitude. Results of 13 previously derived prediction equations using various combinations of height, BW, age, BIA, SF, or CIR measurements as independent variables to predict fat-free mass (FFM), fat mass (FM), and percent body fat (%Fat) were compared with HW. Mean BW decreased from 84.74 to 78.84 kg (P<0.01). As determined by HW, FFM decreased by 2.44 kg (P<0.01), FM by 3.46 kg (P<0.01), and %Fat by 3.02% (P<0.01). The BIA and SF methods overestimated the loss in FFM and underestimated the losses in FM and %Fat (P<0.01). Only the equations utilizing the CIR measurements did not differ from HW values for changes in FFM, FM and %Fat. It was concluded that the BIA and SF methods were not acceptable for assessing body composition changes at altitude.

73. Fusch C, W Gfrörer, C Koch, A Thomas, A Grünert and H Moeller.
Water turnover and body composition during long-term exposure to high altitude (4,900-7,600 m)
Journal of Applied Physiology 80:1118-1125, 1996.

Authors' Abstract

Thirteen healthy subjects (11 men and 2 women; 30.2 ±5.4 yr; 73.5 ±10.3 kg; 178.9 ±10.4 cm; body mass index, 22.9 ±1.6 kg/m^2) participated at the 62-day expedition to Broad Peak (8,047 m), Pakistan. Weight, body water, and water turnover (deuterium dilution and elimination) were measured eight times to assess long-term changes. Body weight fell during the ascent to the base camp [from 73.2 ±9.8 (baseline) to 71.7 ±9.7 kg; P<0.05] and decreased until the end of the base camp stay (66.7 ±7.2 kg; P<0.001). Body compartments changed at different rates. Total body water decreased during the ascent (from 43.1 ±7.3 to 41.0 ±7.7 liters; P<0.05) and remained unchanged until the base camp was reached (41.2 ±6.9 liters; P<0.01), but decreased further during the base camp stay (40.6 ±5.2 liters). Water content of the body (total body water-to-body weight ratio) fell during the ascent (from 58.6 ±3.4 to 55.8 ±4.4%; P<0.01), approached the baseline value during the base camp (57.4 ±4.0 and 58.3 ±5.1%), and increased again until the end of the base camp (60.6 ±3.4 and 60.9 ±4.3%). The compartment of the solids increased during the ascent (from 30.2 ±3.4 to 32.2 ±4.9 kg; P<0.01) and approached the baseline value on arrival at the base camp (30.5 ±4.7 kg). Until the end of the base camp, the compartment of the solids fell (26.9 ±2.6 and 26.1 ±4.0 kg), indicating that weight loss was due to a loss of body solids, presumably mostly fat mass. Water turnover during the pretest period (sea level) was 45 ±7 ml kg^{-1} • day^{-1}; it increased during the ascent (56 ±11 and 60 ±10 ml • kg^{-1} day^{-1}) but remained constant during the base camp stay (63±12, 58±9, and 56±10 ml • kg^{-1} • day^{-1}). It increased during the ascent to Broad Peak (73 ±20 ml • kg^{-1} • day^{-1}; P<0.05) and even more during the descent to civilization (83 ±17 ml • kg^{-1} • day^{-1}; P<0.05).

74. Galster WA and PR Morrison.
Effects of high altitude exposure on components of blood and urine in mountaineers.
International Journal of Biometeorology 18:23-32, 1974.

Authors' Abstract

Physiological correlations with impaired or unimpaired performance at high altitude were sought among 24 blood and urine parameters measured in 50 mountaineers and 21 observers before (preclimb) and after (postclimb) expeditions on Mt. McKinley. Values and per cent changes were compared for five degrees of impairment at high altitude. Average preclimb values were all near established normal levels and no correlations with subsequent involvement at high altitude were found. Postclimb samples contained more Hb, PCV, urea, LDH, and HBD and less bilirubin ($P<0.05$). But no association was found between degrees of altitude impairment and preclimb/postclimb changes in any of the 24 blood and urine parameters. Additional results from samples collected at 4300-m showed "weaker" mountaineers excreted 1/4 as much Na in urine and had 50% more serum FFA concentration than stronger mountaineers.

75. Glatte HV and CL Giannetta.
Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mmHg total pressure. III. Renal response.
Aerospace Medicine 37: 559-562, 1966.

Authors' Abstract

To assess the effects of helium on renal function, four healthy Air Force officers lived for 56 days in a space cabin simulator with a partial pressure of oxygen of 175 mmHg and helium of 74 mmHg at a total pressure of 258 mmHg.

All renal parameters measured during the control and experimental periods failed to reveal any deviation from accepted normals. Studies performed included renal hemodynamics utilizing inulin, PAH, and endogenous creatinine clearances; concentrating and diluting tests; and 24-hour urinary excretion of proteins. In addition, multiple determinations of blood pH and standard bicarbonate utilizing a modified Astrup technique were normal.

Is was concluded that the experimental atmosphere had no adverse effect on renal function.

76. Gotshall RW, DS Miles and WR Sexson.
The combined effects of hypoxemia and mechanical ventilation on renal function.
Aviation, Space, and Environmental Medicine 57:782-786, 1986.

Authors' Abstract

The combined effects of hypoxemia and mechanical ventilation on renal function were investigated in anesthetized dogs. Spontaneously breathing dogs (S) and dogs mechanically ventilated with a volume-ventilator (V) were made hypoxemic by breathing hypoxic gas to achieve P_aO_2 values of 35 and 22 mmHg. At a P_aO_2 of 35 mm Hg, urine output and sodium excretion were increased in both groups. These responses closely followed the blood pressure response, which was greater in the V group. Renal blood flow (RBF), glomerular filtration rate (GFR), and fractional sodium excretion (FNA) were unchanged. At a P_aO_2 of 22 mm Hg, both groups demonstrated a reduction in urine flow, sodium excretion, FNA, RBF, and GFR. However, the mechanism involved was different and ventilator-dependent. At this low P_aO_2, arterial blood pressure was reduced in the S group with no change in renal resistance, while blood pressure increased in the V group with a marked increase in renal resistance as a result of the modification of the cardiovascular effects of lung inflation reflexes by mechanical ventilation. These results indicate that renal function is well-maintained at low P_aO_2 values (35 mm Hg) and reduced at more severe hypoxemia, mainly in response to systemic hemodynamics.

77. Granberg P-O.
Effects of acute hypoxia on renal haemodynamics and water diuresis in man.
Scandinavian Journal of Clinical and Laboratory Investigation 14:Suppl. 63:1-62, 1962.

Author's Abstract

Earlier studies in man and animals concerning the renal function in hypoxia are highly contradictory. The reason for the frequently divergent results is probably due to great differences in the methods and circumstances of the experiments.

The present work is based on investigations of a total of 53 subjects without evidence of renal disease. During water diuresis in a recumbent position the subjects breathed 9 per cent oxygen in nitrogen during 20 minutes. The glomerular flitration rate (C_{IN}), renal plasma flow (C_{PAH}) and urine flow were studied before, during and after the hypoxia breathing. The arterial oxygen saturation and carbon dioxide tension were determined during the experiments.

Thirty-four of the experiments were carried out in a similar way (basic hypoxia cases). In these the oxygen saturation fell on average to 64 per cent during hypoxia breathing, and at this degree of saturation C_{IN} fell to 67 per cent of the initial value. C_{PAH} remained largely unchanged. Urine flow declined markedly in spite of continued hydration and at the end of the hypoxia period was 22 per cent of initial value. It declined further after the hypoxia, whereas the glomerular filtration rate returned to the initial value.

In approximately half of the experiments the urine osmolality and in some subjects the plasma osmolality were determined. U_{OSM} increased during the hypoxia, but did not exceed the plasma level until after the hypoxia period and on average rose only slightly above 400 mOsm/kg H_2O in spite of markedly reduced urine flow. In some cases U_{OSM} rose above 1000 mOsm/kg H_2O whereas in others, including one patient with diabetes insipidus, there was a marked decline of urine flow with only slight increase of U_{OSM}.

Renal vein catheterization was carried out in six subjects. E_{PAH} rose during hypoxia in five of these and was unchanged in one case. The renal oxygen consumption did not change notably in these experiments when the arterial oxygen saturation fell.

Comparisons of renal function at different oxygen saturations, and experiments with hyperventilation of hypoxic gas and air support the view that the hypoxia and not the concomitant hypocapnia was the cause of the recorded changes.

In the present investigations of the renal function on man during water diuresis it was found that on acute hypoxia with a fall of arterial oxygen saturation to about 60 per cent:

(1) the glomerular filtration rate fell more than the renal plasma flow;
(2) the extraction of PAH did not fall;
(3) the renal oxygen consumption did not perceptibly change;
(4) the urine flow declined markedly;
(5) the decline in the urine flow was probably due partly to an increased secretion of antidiuretic hormone and partly to reduced glomerular filtration rate;
(6) the hypoxia and not the simultaneously appearing hypocapnia was the cause of the changes found.

78. Greenleaf JE, EM Bernauer, WC Adams and L Juhos.

Fluid-electrolyte shifts and $\dot{V}O_{2\,max}$ in man at simulated altitude (2,287 m). *Journal of Applied Physiology* 44:652-658, 1978

Authors' Abstract

Six trained distance runners were studied during an 8-day dietary control (C) period at sea level (24 m, 758 Torr), followed by 8 days at 2,287 m (576 Torr) in an altitude chamber (A), and 4 days recovery (R) at sea level. The purpose of the study was to determine whether reduction in maximal oxygen uptake ($\dot{V}O_{2\,max}$) during early exposure to the reduction in P_{O_2} at altitude is accentuated 1) by reduced plasma volume (PV), or 2) to a more generalized negative water balance. For 2 mo prior to the study the men ran 15 km/day, and during the study ran 16 km/hr for 1 h each day. Mean ±SE $\dot{V}O_{2\,max}$ was 4.75 ±0.23 l/min in C, 4.05 ±0.22 l/min at A (Δ = -14.7%, P<0.05), and 4.68 ±0.22 l/min during R. Basal blood volume, PV, and red blood cell (RBC) volume were essentially constant during C and A, and there was no change in fluid balance at A. During maximal exercise the mean calculated change (shift) of PV was -6% during C, but increased to between -11% and -15% at A and coincided with the reduction of -13% to -15%

in $\dot{V}O_{2\,max}$. On the 1st day of R (R+1) $\dot{V}O_{2\,max}$ returned to sea-level values, but Δ PV was still -15%. However, the latter returned to control levels on R+2. The shift of plasma Na, Cl, and osmotic contents followed the shift in PV, the K response was variable, and total protein and Hb content shifts were relatively stable (Δ = ±4%). The exaggerated PV and electrolyte shifts during maximal exercise at altitude perhaps reflect alterations in cellular membrane permeability, but neither amplified PV shifts nor negative water balance contribute to the reduction in $\dot{V}O_{2\,max}$ at altitude.

79. Grigor'yev AJ, VI Korol'kov, GI Kozyrevskaya and MA Dotsenko.
Effect of hypoxia on fluid-electrolyte metabolism and renal function in man as related to different degrees of motor activity.
Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 5:10-14, 1979.

Authors' Abstract

It was demonstrated that a prolonged (24 days) bed rest at altitudes of 2200 m and 3200 m as well as at sea level was accompained by an increased renal excretion of fluids and osmotically active substances, including electrolytes. Exercises done during bed rest induced a smaller increase of the renal excretion of sodium and potassium. However, as bed rest continued the differences between the groups of test subjects disappeared. The levels of hypoxia and exercises used in the study proved inefficient to prevent changes in the fluid-electrolyte metabolism occurring during bed rest.

80. Guillard JC and J Klepping.
Nutritional alterations at high altitude in man.
European Journal of Applied Physiology 54:517-523, 1985.

Authors' Abstract

During the French 1980 Mount Pabil (7,120 m) Expedition, a study was made of four altitude-acclimatised climbers (age 36.5 ±3.6 years: $\dot{V}O_{2\,max}$ 50.5 ±3.1 ml kg^{-1}). Intake of various nutrients, body weight, skinfold thicknesses as indices of body composition, and water and nitrogen balances, were recorded before, and during high altitude exposure, and again after the return to low altitude.

There was a significant (35-57%) reduction in total caloric intake at high altitude. Body weight decreased progressively, mainly due to a reduction in body fat. The subjects apparently remained in water balance, while the nitrogen balance was always negative during high altitude exposure.

The significant nutritional alterations were mainly observed above 6,000 m. They are discussed with respect to changes in feeding patterns and in hormonal status of the climbers accompanying hypoxia and other stressors proper to high altitude.

81. Gunga H-C, K Kirsch, F Baartz, H-J Steiner, P Wittels and L Röcker.
Fluid distribution and tissue thickness changes in 29 men during 1 week at moderate altitude (2,315 m).
European Journal of Applied Physiology 70:1-5, 1995.

Authors' Abstract

To quantify fluid distribution at a moderate altitude (2,315 m), 29 male subjects were studied with respect to tissue thickness changes [front (forehead), sternum, tibia], changes of total body water, changes of plasma volume, total protein concentrations (TPC), colloid osmotic pressure (COP), and electrolytes. Tissue thickness at the forehead showed a significant increase from 4.14 mm to 4.41 mm 48 h after ascent to the Rudolfshuette (2,315 m) (P<0.05). At 96 h after ascent the tissue thickness at the tibia was decreased to 1.33 mm compared to the control value of 1.59 mm (P<0.01). Body mass increased from 75.5 kg (control) to 76.2 kg on the last day (P<0.05) and body water from 44.21 to 45.01 during the week (P<0.01). The accumulation fluid in the upper part of the body was paralleled by a decrease in TPC and COP. At 48 h after the ascent COP dropped from 29.5 mmHg to 27.5 mmHg (P<0.01). After 96 h at moderate altitude COP was still significantly decreased compared to the control level. At 1.5 h after the return from the Rudolfshuette in Saalfelden (744 m) COP was back to the control values. The TPC also showed an initial drop from 7.75 g • dl^{-1} to 7.48 g • dl^{-1} after 48 h at altitude and

remained below the control value during the whole week ($P<0.01$). It seems from our study that even with exposure to moderate altitude, measurable fluid shifts to the upper part of the body occurred which were detected by our ultrasound method.

82. Hack D, NW Levin, B Goldberg, SM Perold and A Rubenstein.
Serum electrolytes at high altitude.
South African Journal of Medical Science 29:11-16, 1964.

Annotation

Purpose

To establish values for some commonly estimated blood constituents in healthy young people living in Johannesburg (altitude approximately 5,250 feet above sea level) and to compare them with those measured in subjects living in Cape Town (sea level).

Methods

The subjects studied were healthy medical students, 68 being in the Johannesburg group and 38 in the Cape Town group. Blood specimens were obtained at 8 a.m. with the subjects fasting; the estimations were carried out over a period of two weeks to check the effects of storage; some samples were estimated at the beginning and at the end of this period. No differences were found in the results obtained.

Results

The mean plasma carbon dioxide content and serum sodium concentrations were significantly lower and the haemoglobin and serum chloride concentrations significantly higher in the group resident in Johannesburg compared to the group at sea level. There was no significant difference between the serum potassium and plasma phosphorus concentrations.

Conclusions

This study confirms other reports that the concentration of certain electrolytes in subjects at high altitudes is significantly different from those measured in persons living at sea level. The reduction in plasma carbon dioxide content may be due to increased resting ventilation which occurs at 5,750 feet. The resulting respiratory alkalosis is then compensated for by a decrease in plasma bicarbonate level. Long term compensation probably occurs mainly in the kidney with increased tubular reabsorption of chloride in preference for bicarbonate.

83. Hackett PH, ML Forsling, J Milledge and D Rennie.
Release of vasopressin in man at altitude.
Hormone Metabolic Research 10:571, 1978.

Authors' Abstract

While Forsling and Milledge (1977) found that 4 h exposure to 10.5% oxygen (equivalent to 5490 m altitude) had little effect on vasopressin release in man, the result of prolonged exposure is not clear. Excessive fluid retention and hence possibly vasopressin could contribute to the various forms of oedema seen at altitude. These include pulmonary, cerebral and peripheral oedema as defined previously (Hackett, Rennie and Levine 1976). The purpose of the present study was to investigate the release of vasopressin in the human at altitude with a view to a greater understanding of the pathophysiology of acute mountain sickness (AMS) and altitude oedema.

The observations were performed at Pheriche, Nepal (altitude, 4243 m) in the Himalayas on 14 subjects. These included 7 control subjects (5 female) who showed no symptoms, 2 subjects with AMS (both female) and 4 subjects additionally with high altitude pulmonary oedema (2 female). On sampling, the blood was immediately centrifuged, the plasma separated and maintained in liquid nitrogen until analysed in London. Hormone determination was performed on extracted plasma as described by Chard and Forsling (1976).

The results are summarised in the figure. The plasma vasopressin in the control group was 1.1 ±0.15 μU/ml (±SEM, n = 7) as compared with 0.7 ±0.17 μU/ml (n = 10) in a previous study at sea level and there was no difference in vasopressin concentration between the ascent and the descent from 5,300 m. Thus altitude alone did not appear to affect the release of vasopressin. The results were similar to those seen with acute hypoxia, when a value of 1.1 μU/ml was recorded (Forsling and Milledge 1977). Plasma vasopressin was significantly elevated in those subjects with AMS to a mean concentration of 2.2 ±0.5 (n =

7, $p<0.01$). The results of Singh, Malhotra, Khanna, Nanda, Purshattam, Upadhyay, Radhakrishnan and Brahmachari (1974) suggest a similar trend. It was also noted that five of the climbers with AMS also suffered with peripheral oedema as indicated in the figure. The present studies do not indicate whether the increased vasopressin secretion was a primary change and a major factor in the pathophysiology of AMS or secondary to a shift in fluid from the vascular bed or indeed to stress. The concentrations recorded would have been sufficient to cause a degree of water retention provided that the renal sensitivity to vasopressin was unchanged.

84. Hackett PH, D Rennie, RF Grover and JT Reeves.
Acute mountain sickness and the edemas of high altitude: a common pathogenesis?
Respiration Physiology 46:383-390, 1981.

Authors' Abstract

Within days of ascent to high altitude when symptoms of acute mountain sickness (AMS) are common, pulmonary and cerebral edema may develop. Although peripheral edema of the hands, face or feet may also appear, its association with AMS is unclear. In addition, persons with high altitude pulmonary edema often report an antidiuresis. Hence, altitude sickness appears to result from abnormalities in the handling of body water. To test this hypothesis, we studied 102 men and women who were trekking in the Mount Everest region of Nepal. Most were seen both at low (1377 m) and at high (4243 m) altitude. Severity of AMS was measured by an established Symptom Score derived from a questionnaire and physical examination. Change in body water was inferred from change in body weight in less that 10 days. Peripheral edema was assessed separately by physical examination. AMS Symptom Score correlated directly with weight change; those who remained well lost weight, whereas increasing signs and symptoms of AMS occurred in those with increasing weight gain. The symptomatic subjects also developed peripheral edema and reported decreased urinary output.

These findings support the hypothesis that with rapid ascent to high altitude, abnormalities in the handling of body water, with antidiuresis, result in fluid retention (weight gain) manifest as peripheral, pulmonary, and/or cerebral edema.

85. Hackett PH, D Rennie, SE Hofmeister, RF Grover, EB Grover and JT Reeves.
Fluid retention and relative hypoventilation in acute mountain sickness.
Respiration 43:321-329, 1982.

Authors' Abstract

The presence of pulmonary, cerebral, and/or peripheral edema in acute mountain sickness (AMS) implies a derangement in the body's handling of water. Previously, we demonstrated water retention and increased symptoms of AMS when hypocapnia was prevented in subjects exposed to simulated high altitude. This led us to the hypothesis that upon ascent to high altitude, those persons who fail to increase their ventilation adequately and hence do not become hypocapnic will retain water reflected as weight gain and will develop AMS. To test this hypothesis, we studied in Kathmandu, Nepal (1,377 m) 42 healthy western tourists; all were restudied in Pheriche (4,243 m) within 6 days of exposure to high altitude. Symptoms of AMS were highly correlated ($p<0.001$) with weight change, suggesting that persons becoming symptomatic retained fluid. On going from low to high altitude, those persons who lost weight and remained well increased their resting ventilation, whereas those who gained weight did not ($p=0.03$). This relative hypoventilation in the latter group was confirmed by higher values of P_{CO_2} (heated hand vein blood) and lower values of arterial saturation (ear oximeter) at Pheriche. Vital capacity measured in Kathmandu was correlated with arterial saturation at Pheriche ($p=0.02$); persons with low vital capacity were more hypoxemic with more symptoms of AMS. We conclude that relative hypoventilation and weight gain appear early in the development of AMS suggesting links between altitude hypoxia, hyperventilation, hypocapnia, and the body's handling of water.

86. Hackney AC, JT Coyne, R Pozos, S Feith and J Seale.
Validity of urine-blood hydrational measures to assess total body water changes during mountaineering in the sub-Arctic.
Arctic Medical Research 54:69-77, 1995.

Authors' Abstract

Mountaineering involves high altitude and cold exposure which are each associated with significant levels of dehydration (via altitude-cold diuresis, high energy expenditures, and poor access to water). The purpose of this study was to identify and validate urine and blood indices of dehydration as compared to changes in total body water (which served as the reference standard). Male subjects (n=10) were studied during a 14 day mountaineering expedition in the sub-Arctic during which they climbed to an altitude of 5245 ± 229 m (mean ±SE). Daily activity consisted of approximately 10-15 hours skiing, hiking, and performing mountaineering tasks with heavy loads (>30 kg). Various measurements were made immediately before ascending (Pre) and after descending (Post) the mountain: body weight (Bw) and composition (%Fat), urine specific gravity (USG), urine protein (UP), plasma electrolytes (K^+, Cl^-, Na^+), plasma proteins (PP), plasma and urinary osmolality (UOsm), hematocrit (Hct), hemoglobin (Hb), blood urea nitrogen (BUN), plasma aldosterone, and total body water (TBW determined via deuterium oxide). Post the expedition significant ($p<0.05$) decreases were observed in Bw, and %Fat, while significant increases were found in Na^+, K^+, USG, UOsm and UP. TBW was slightly reduced, however, changes were non-significant (Pre = 52.9 ±1.2 L vs Post = 52.6 ±1.3 L). USG is often used to monitor hydration status in field settings; however, no significant correlations were found between changes in TBW and USG, nor between changes in TBW and other typical urinary indicators of dehydration. The strongest correlations with alterations in TBW were the changes in Na^+, Cl^-, and Hct ($p < 0.05$). These data suggest that during a mountaineering expedition standard urinary indices of hydration status may be of little benefit in determining the presence or magnitude of changes in TBW content.

87. Hannon JP and KSK Chinn.
Effects of high altitude on body fluid volumes.
Federation Proceedings 26:719, 1967. (Abstract).

Authors' Abstract

Nine young male subjects were studied initially at low altitude (San Antonio, Texas) and subsequently during 15 days' exposure at high altitude (Pikes Peak - 14,110 ft). From a low altitude value of 2.99 1., plasma volume (Evans Blue) decreased progressively at high altitude, reaching a value of 2.40 l. on the 15th day of exposure. Calculated blood volume decreased similarly. During the first 8 days of exposure, extracellular volume (NaSCN space) was reduced from 17.34 l. to 13.79 l. A slight recovery, 15.21 l., was observed on the 15th day. Total body water measurements (4-aminoantipyrine space) indicated a slight dehydration during the first day; i.e. from 38.52 l. to 37.67 l., and a slight hydration to 39.29 l. on the 15th day of exposure. Measurements of D_2O space yielded unreliable data. Calculations of intracellular space showed a progressive increase from 21.19 l. to 24.17 l, over the first 8 days at altitude. Body density measurements showed weight loss at high altitude was due to a loss of fat.

88. Hannon JP, KSK Chinn and JL Shields.
Effects of acute high-altitude exposure on body fluids.
Federation Proceedings 28:1178-1184, 1969.

Annotation

Purpose

To study the mechanisms affecting hemoconcentration at high altitude.

Methods

Nine soldier volunteers age 20 to 24 were transported to Pikes Peak (14,100 ft) after control base measurements were taken at low altitude. At Pikes Peak the following measurements were taken: total body water content, intra-and extracellular volumes, plasma volume, interstitial volume, and total extracellular cation concentration.

Results

Body water measurements based upon

4-aminoantipyrine dilution and body density measurements showed little or no change during the first week at altitude, and a small ($p<0.05$) increase during the 2nd week. Plasma volume, determined with the Evans blue procedure, decreased after two weeks by 600 ml or 20%. After 7 days over 3.5 L, or 20% of extracellular fluid, is transferred to the intracellular space. Between 7 and 14 days exposure there was a slight but significant recovery of the interstitial and extracellular fluid volumes, whereas the intracellular fluid volume remained increased. This recovery, attributable to the slight increase in total body water which was noted above, occurred in the same time period. Finally, total extracellular cation level declined during the first week with a shift (recovery) during the second week. This was primarily attributable to loss of sodium, a predominantly extracellular cation.

Conclusions

The cause of these altitude-induced changes in extra- and intra-cellular fluid volumes has yet to be resolved; in fact, most explanations are still speculative. One intriguing possibility is found in the body electrolyte changes seen during high altitude exposure. A reduction in extracellular cations (and osmotic activity) would be consistent with a movement of water from the extra- to the intra-cellular compartment. The cation as well as the anion levels in these two compartments, particularly the intracellular, obviously need further investigation before this suggested mechanism can be verified.

89. Hannon JP, KSK Chinn and JL Shields.

Alterations in serum and extracellular electrolytes during high-altitude exposure.

Journal of Applied Physiology 31:266-273, 1971.

Authors' Abstract

The concentration and total quantity of electrolytes in serum and extracellular (thiocyanate) space were measured in nine soldiers, initially in San Antonio, Texas (200 m), and subsequently after 1, 3, 7, and 14 days' exposure in Pikes Peak (4,300 m). Altitude exposure caused a total reduction in serum bicarbonate concentration of 7.0 mEq/L. Most of this loss was replaced by an increase in chloride concentration, with minor contributions from protein anion and inorganic phosphate. The serum concentrations of sodium and calcium were unaffected by altitude exposure while the concentrations of potassium and magnesium were slightly elevated. Because of marked reduction in extracellular space, total extracellular electrolytes principally sodium, chloride, and bicarbonate, were similarly reduced. Total body water (4-aminoantipyrine space), on the other hand, was slightly elevated, hence calculated intracellular space was markedly elevated. It was concluded that this high-altitude transfer of water from the extra- to the intracellular space was caused by the osmotic effects associated with a transfer of electrolytes from the extra- to the intracellular compartment.

90. Hannon JP, JL Shields and CW Harris.

Anthropometric changes associated with high altitude acclimatization in females.

American Journal of Physical Anthropology 31:77-84, 1969.

Authors' Abstract

The anthropometric effects of prolonged high altitude exposure were studied in eight college women who lived on the summit of Pikes Peak (14,100 ft) for 2.5 months. Acclimatization to altitude was associated with a decrease of skinfold thickness and a reduction in limb circumference, but little change in body weight. It was concluded that these changes reflected a loss of subcutaneous fat during the period of altitude exposure. Altitude exposure did not produce any alterations in trunk circumference at the umbilicus or buttocks, but it did cause an increase in the inspiratory chest circumference at the axillary level and a reduction in expiratory chest circumference at the subscapular level.

91. Hannon JP, CW Harris and JL Shields.

Alterations in the serum electrolyte levels of women during high altitude (4,300 m) acclimatization.

International Journal of Biometeorology 14:201-209, 1970.

Authors' Abstract

Eight University of Missouri (230 m) college women were exposed for a period of 65 days to an elevation of 4,300 m on Pikes Peak. During the first week of altitude exposure marked increases in the serum levels of chloride, phosphate, proteinate and calcium and marked decreases in the serum levels of sodium, potassium, magnesium and estimated bicarbonate were observed. During the remainder of the altitude sojourn chloride, phosphate, potassium, and magnesium reverted toward the initial low altitude value. Serum calcium levels, however, remained elevated during this latter period while sodium levels continued to decrease and proteinate levels continued to increase. There was little or no recovery of the estimated bicarbonate decrement as the period of exposure was prolonged. Two weeks after the subjects returned to Missouri some but not all of the electrolytes returned to their initial levels. Those not recovering completely included calcium, chloride, proteinate and estimated bicarbonate.

92. Hannon JP, GJ Klain, DM Sudman and FJ Sullivan.
Nutritional aspects of high-altitude exposure in women.
American Journal of Clinical Nutrition 29:604-613, 1976.

Authors' Abstract

The nutrient intake and urinary excretion characteristics of eight young university women were studied over a 4-day period at low altitude (140 m) and subsequently over a 7-day sojourn on Pikes Peak (4,300 m). High-altitude exposure was associated with a transient decrease in the consumption of protein, carbohydrate, fat, sodium, calcium, phosphorus, vitamin A, riboflavin, thiamin, and niacin and a more sustained decrease in the consumption of potassium and ascorbic acid. In most instances minimal values were observed during the first 3 days of exposure. The carbohydrate fraction of energy intake was increased at the expense of fat during this time period. Individual hypophagic responses appeared to be related to severity of acute mountain sickness. Altitude had no effect on water consumption but did lead to an average body weight loss of 1kg. Urinary measurements revealed a marked oliguria during the entire sojourn. These measurements also showed the first 3 days to be associated with a net loss of body nitrogen and sodium. During this time period body potassium and phosphorus were conserved, and probably increased. The urea fraction of total urinary nitrogen was not affected by altitude exposure, nor was the daily excretion of uric acid and creatinine. Ammonia excretion, however, was reduced to 50% of the low-altitude value and remained at this level throughout the sojourn. With a few exceptions, the qualitative characteristics of altitude hypophagia in women were similar to those reported for men. Quantitatively, however, the responses were much more transient in women.

93. Hannon JP, JL Shields and CW Harris.
Effects of altitude acclimatization on blood composition of women.
Journal of Applied Physiology 26: 540-547, 1969.

Authors' Abstract

The effects of altitude acclimatization on blood composition were studied in eight University of Missouri (elev 700 ft) coeds who lived on the summit of Pikes Peak (elev 14,000 ft) for 10 weeks. During the period of altitude exposure the following changes were observed: a transient increase in heart rate, the maximum being reached on the 1st day of exposure; an early rapid increase in hematocrit and hemoglobin which later became more gradual; an early and sustained reduction in plasma volume; a rapid initial increase and a more gradual later increase in plasma protein concentration which was attributable to elevations in both the albumin and the globulin fractions; a sustained decrease in the albumin-to-globulin ratio; a slight but sustained increase in serum oncotic pressure; a slight but sustained decrease in blood water content and serum and osmolarity; and finally, an unaltered total leukocyte count, but a significant increase in lymphocytes and significant decrease in monocytes. It is concluded that the hematopoietic response to altitude is markedly less in women than that usually observed in men. In women at least, dietary iron supplementation enhances the rate of hematocrit increase at altitude. And finally, the loss of

plasma volume is felt to be real and not due to simple dehydration.

94. Hansen JM, NV Olsen, B Feldt-Rasmussen, I-L Kanstrup, M Déchaux, C Dubray and J-P Richalet.
Albuminuria and overall capillary permeability of albumin in acute altitude hypoxia.
Journal of Applied Physiology 76:1922-1927, 1994.

Authors' Abstract

The mechanism of proteinuria at high altitude is unclear. Renal function and urinary excretion rate of albumin (U_{alb}) at rest and during submaximal exercise, and transcapillary escape rate of ^{125}I-labeled albumin (TER_{alb}), were investigated in 12 normal volunteers at sea level and after rapid and passive ascent rate to 4,350 m. The calcium antagonist isradipine (5 mg/day; n=6) or placebo (n=6) was administered to abolish hypoxia-induced rises in blood pressure. Lithium clearance and urinary excretion of β_2-microglobulin were used to evaluate renal tubular function. High altitude increased U_{alb} from 2.8 to >5.0 µg/min in both groups (P<0.05). In the placebo group, high altitude significantly increased filtration fraction (P<0.05), but this response was abolished by isradipine. Lithium clearance and urinary excretion of β_2-microglobulin remained unchanged by hypoxia in both groups. Exercise did not reveal any further renal dysfunction. In both groups, high altitude increased TER_{alb} from 4.8 to >6.7% /h (P<0.05). In conclusion, acute altitude hypoxia increases U_{alb} despite unchanged tubular function and is independent of effects of isradipine on filtration fraction. The elevated TER_{alb} suggests an overall increase in capillary permeability, including the glomerular endothelium, as the critical factor in high-altitude induced albuminuria.

95. Harber MJ, JD Williams and JJ Morton.
Antidiuretic hormone excretion at high altitude.
Aviation, Space, and Environmental Medicine 52:38-40, 1981.

Authors' Abstract

Urinary excretion of electrolytes, creatinine, urea, and antidiuretic hormone-measured as arginine vasopressin (AVP) by radioimmunoassay-was investigated in eight Himalayan mountaineers during ascent on foot from 1900-5400 m. Specimens were collected from each individual whenever urine was voided, preserved with 1% boric acid, and subsequently pooled to give samples representative of 24-h collections. AVP was found to be reasonably stable under simulated conditions of storage. In all subjects, the observed AVP excretion rates were mostly in the lower region of the normal range and there was generally no correlation with altitude, urine osmolality, electrolyte excretion, or occurrence of AMS symptoms-even in a fatal case of cerebral oedema. It is concluded that AVP does not play a primary role in the changes in fluid balance which accompany either acclimatization to high altitude or the onset of AMS.

96. Heyes MP, MO Farber, F Manfredi, D Robertshaw, M Weinberger, N Fineberg and G Robertson.
Acute effects of hypoxia on renal and endocrine function in normal humans.
American Journal of Physiology 243:R265-R270, 1982.

Authors' Abstract

The effects of hypoxia upon renal and endocrine function are unclear. Normal water loaded subjects were exposed to hypoxia for 1 h (inspired PO_2 = 74 Torr) in a decompression chamber (5,100m, n = 8) or by breathing 10.5% oxygen at ambient pressure (n = 4). In four of eight subjects exposed to hypobaric hypoxia: urine flows ($\dot{V}$) decreased (mean = 56%), urine osmolality increased (340%), plasma arginine vasopressin (AVP) increased (2,700%), plasma cortisol increased (256%), and mean blood pressure (BP) decreased (18%). $\dot{V}$ correlated inversely with AVP (r = -0.71, P<0.01) while AVP increases correlated with falls in mean BP (r = -0.72. P<0.05). Similar results were observed in the subjects exposed to normobaric hypoxia. Plasma aldosterone fell in the four subjects who maintained $\dot{V}$ on exposure to hypobaric hypoxia, but plasma renin activity did not change. In both groups prolactin levels were

variable and solute and creatinine excretion were unchanged. No changes were observed in controls or in subjects exposed to hypobaria alone. Acute hypoxic exposure may produce significant hypotension with consequent increased AVP secretion resulting in diminished $\dot{V}$.

97. Heyes MP and JR Sutton.
High altitude ills: a malady of water, electrolyte and hormone imbalance?
Seminars in Respiratory Medicine 5:207-212, 1983.

Authors' Abstract

Evidence suggests that water retention occurs in individuals who develop AMS on acute exposure to altitude. The predisposed person also appears to underventilate. Although increases in AVP are associated with AMS, these may be the result of AMS rather than a cause. Extensive studies of the renin-angiotensin-aldosterone system have not shown any consistent relationship with AMS. Nevertheless, a decrease in angiotensin-converting enzyme activity may have more important implications for edema formation. This decrease would result in an impaired ability to degrade bradykinin, a potent edematic agent, that could be important for the already vulnerable hypxic lung and might contribute to systemic and cerebral edema.

98. Hogan III RP, TA Kotchen, AE Boyd III and LH Hartley.
Effect of altitude on renin-aldosterone system and metabolism of water and electrolytes.
Journal of Applied Physiology 35:385-390, 1973.

Authors' Abstract

Plasma renin activity and urinary aldosterone excretion were studied in 10 normal male volunteer test subjects between the ages of 19 and 23 who were exposed to a simulated altitude of 12,000 ft (483 mm Hg) in a hypobaric chamber for 72 hr. Subjects consumed a controlled 160 mEq sodium, 60 mEq potassium diet throughout the study. Plasma renin activity and urinary aldosterone excretion were decreased. Subjects retained potassium, lost sodium, and had mild water and weight losses. Increased insensible loss was primarily responsible for the negative water balance. Test subjects who experienced the most severe symptoms of acute mountain sickness also showed the greatest decrease in aldosterone excretion at altitude. Data presented are consistent with the conclusion that aldosterone secretion at altitude follows usual control mechanisms, contrary to previous reports. It is postulated that the observed depression in renin release is secondary to decreased renovascular resistance and increased renal blood flow.

99. Honig A.
Salt and water metabolism in acute high altitude hypoxia: Role of peripheral arterial chemoreceptors.
News in Physiological Science 4:109-111, 1989.

Author's Abstract

Mammals acutely exposed to hypobaric hypoxia establish a lower plasma volume by increasing urine excretion or by reducing salt and water intake. These responses are of adaptive value, for by concentrating available hemoglobin they increase O_2-binding capacity of the blood. The reactions of sodium metabolism in arterial hypoxia are controlled by peripheral arterial chemoreceptors.

100. Hoon RS, SC Sharma, V Balasubramanian and KS Chadha.
Urinary catecholamine excretion on induction to high altitude (3,658 m) by air and road.
Journal of Applied Physiology 42:728-730, 1977.

Authors' Abstract

In a preliminary pilot study we had reported a significant difference in urinary catecholamine excretion between symptomatic and asymptomatic individuals inducted to high altitude by air. The present study covers slower induction by road; 25 lowlanders ascended from 1,800 to 3,658 m in 50 h and 33 similar subjects covered the journey in 6 h. They were studied according to the protocol used in the initial study. None of the 58 subjects inducted by road developed symptoms of high-altitude illness. Their urinary catecholamine excretion remained normal during the 10 days' stay at high altitude. These findings lend support to our earlier contention that there might be a relationship between

increased sympathoadrenal activity and high-altitude illnesses.

101. Hoon RS, SC Sharma, V Balasubramanian, KS Chadha and OP Mathew.
Urinary catecholamine excretion on acute induction to high altitude (3,658m).
Journal of Applied Physiology 41:631-633, 1976.

Authors' Abstract

Fifty healthy male volunteers, 21-34 yr of age, normally resident at altitudes less than 1,000 m, were airlifted to 3,658 m. Urinary excretion of catecholamines was measured at sea level (198 m) and on the 1st, 2nd, 4th, and 10th day of a stay at high altitude. The symptoms observed on exposure to high altitude were assigned arbitrary scores. The volunteers could, on this basis, be divided into "symptomatic" and "asymptomatic" groups. The two groups showed a markedly different pattern of urinary catecholamines excretion on exposure to high altitude and on return to sea level. Significant increase in the catecholamine excretion was observed in the symptomatic group only. A possible role for enhanced sympathoadrenal activity in the etiopathogenesis of high-altitude illnesses is postulated.

102. Hornbein TF.
Adrenal cortical response to chronic hypoxia.
Journal of Applied Physiology 17:246-248, 1962.

Author's Abstract

Although acute oxygen lack causes increased adrenal cortical activity, there is evidence that continued exposure to hypoxia is accompanied by a return of adrenal cortical function to its sea level status. To evaluate the adrenal cortical response in men living for 14-21 days above 21,000 ft., urinary output of 17-hydroxycorticoids was measured in ten members of a Himalayan mountaineering expedition and compared to values obtained subsequently at sea level. No significant difference in 17-hydroxycorticoid output was observed between the two altitudes. The response of four subjects to the administration of Su-4885 (Methopyrapone) showed that the pituitary-adrenal cortical system was still capable of response to additional stimulation.

103. Houston CS and RL Riley.
Respiratory and circulatory changes during acclimatization to high altitude.
American Journal of Physiology 149:565-588, 1974.

Authors' Abstract

Detailed studies of the respiratory and circulatory changes which occur during the process of acclimatization to oxygen lack were made on four men exposed to gradually increasing simulated altitude during one month in a low pressure chamber.

The data obtained strengthen the concept that acclimatization consists of a series of integrated adaptations which tend to restore the oxygen pressure of the tissues toward normal sea level values despite the lowered pO_2 of the atmosphere.

The transfer of oxygen from inspired air to tissue cells can be conveniently divided into several stages which together comprise the oxygen transport system. A theoretical mean value for the capillary oxygen pressure has been introduced to make possible a more quantitative evaluation of circulatory factors than heretofore possible.

The reduction in the pO_2 gradient between inspired air and mean capillary blood was due mostly to the shape of the oxyhemoglobin dissociation curve and to an increase in pulmonary ventilation; increase in cardiac output, increase in the diffusion constant of the lung, and increase in oxyhemoglobin capacity were less important factors.

The same pulmonary and circulatory changes which caused an increase in pO_2 necessarily caused a decrease in pCO_2, and an initial effect of the decrease in pCO_2 was an increase in the alkalinity of the blood. Further changes occurred, as acclimatization progressed, to counteract this respiratory alkalosis. The fall in blood bicarbonate reflected the extent of these changes which included a net increase in the other negative ions and probably a net decrease in the positive ions. These changes comprised secondary factors in acclimatization. There was no evidence that cellular metabolism decreased as part of the acclimatization process, since the oxygen consumption remained the same at

altitude as at sea level, both during rest and during standard work. Since clinical evidence indicated that the subjects were moderately anoxic, it appears that cellular function was impaired by low pO_2, even though the amount of oxygen used by the cells remained normal.

104. Houston CS, JR Sutton, A Cymerman and JT Reeves.
Operation Everest II: man at extreme altitude.
Journal of Applied Physiology 63:877-882, 1987.

Authors' Abstract

Rapid ascent to high altitude may cause serious problems for climbers, skiers, and aviators. In contrast, gradual ascent enables humans to function where the unacclimatized cannot. To examine changes in the O_2 transport system that produce acclimatization, eight men were taken in a decompression chamber (without other stresses experienced on high mountains) to a simulated altitude of 8,840m (29,028 ft, ambient PO_2 = 43 Torr) in 40 days. Maximal O_2 uptake fell to 1.21 L/min, and arterial pO_2 and pCO_2 were 30 and 11 Torr, respectively, with pH of 7.56. Many sophisticated studies were done: Swan-Ganz catheterization and inert gas diffusion studies at three altitudes showed that normal cardiac function persisted, pulmonary vascular resistance increased and at extreme altitude was not lowered by O_2, and pulmonary ventilation-perfusion mismatch increased, though variably. This appears to be an important factor limiting performance at extreme altitude. This paper presents the background, general approach, and a summary of major observations reported in detail in other papers.

105. Howell A and DH Cove.
Birmingham Medical Research Expeditionary Society 1977 Expedition: The diuresis and related changes during a trek to high altitude.
Postgraduate Medical Journal 55: 471-474, 1979.

Authors' Abstract

Continuous 24-hr urine collections were made by 17 subjects during a trek to 5400 m. Fluid intake was recorded by diary. Weight and fat folds were measured daily. The results were compared with daily measurements of packed cell volume (PCV) and reticulocyte count. Early fluid retention was matched by a fall in PCV. There was a diuresis with negative fluid balance towards the end of the ascent and again early in descent. There was a slight trend for fluid retention to occur in those most affected by acute mountain sickness but the effect was not marked.

106. Hoyt RW, MJ Durkot, GH Kamimori, DA Schoeller and A Cymerman.
Chronic altitude exposure (4300 m) decreases intracellular total body water in humans.
In: Hypoxia and Mountain Medicine. Proceedings of the 7th International Hypoxia Symposium, edited by JR Sutton, G Coates, and CS Houston. New York: Pergamon Press, 1992. p.306. (Abstract).

Authors' Abstract

There are several reports that chronic altitude exposure increases intracellular fluid volume (ICF) with no change in total body water volume (TBW). However, our animal experiments have not supported this position. To further investigate altitude-induced body fluid redistribution, nine adult males (23 to 33 yr) were studied before and after 10 days at 4300 m elevation. Apparent extracellular fluid volume (ECF_a) and TBW were measured by NaBr and $H_2{}^{18}O$ dilution, respectively. Bromide space was corrected for tracer distribution outside the ECF. The percent change in plasma volume (PV) was estimated from changes in hemoglobin concentration and hematocrit. Apparent ICF was calculated ($ICF_a = TBW - ECF_a$). There were significant ($p<0.05$) decreases in body mass (86.6 ±4.6 vs. 82.2 ±4.3 kg) (mean ±SEM) , TBW (47.6 ±2.2 vs. 45.9 ±1.9 l), ICF_a (19.3 ±1.4 vs. 16.3 ±1.3 l), and PV (-20.0 ±1.4%). The ECF_a did not change (28.2 ±1.0 vs. 29.6 ±1.6 l) ($p>0.05$). Prolonged altitude exposure in humans resulted in both cellular hypohydration and decreased TBW.

107. Hoyt RW, TE Jones, CJ Baker-Fulco, DA Schoeller, RB Schoene, RS Schwartz, EW Askew and A Cymerman.
Doubly labeled water measurement of human energy expenditure during exercise at high altitude.
American Journal of Physiology 266:R966-R971, 1994.

Authors' Abstract

Estimates of total daily energy expenditure (TDEE) by the doubly labeled water (DLW, $^2H_2{}^{18}O$) and intake balance (I-B) methods were compared in six male soldiers studied over 6 days that included 5 days of strenuous winter exercise at 2,500- to 3,100-m elevation. Use of body energy stores [-9.54 ±1.54 (SD) MJ/day or -2,280 ±368 kcal/day] was estimated from changes in body weight, body density (hydrodensitometry), and total body water ($H_2{}^{18}O$ dilution). The subjects wore computerized activity monitors and kept daily records of ration consumption (9.87 ±3.60 MJ/day or 2,359 ±860 kcal/day). Accuracy of individual DLW and I-B TDEE values was estimated from the correlations of TDEE with fat-free mass (FFM) or total weight (body wt + load). The DLW and I-B estimates of TDEE differed by -12.0 to 15.2% but provided comparable estimates of group mean TDEE (DLW = 19.07 ±2.37 MJ/day or 4,558 ±566 kcal/day; I-B = 19.41 ±3.72 MJ/day or 4,639 ±889 kcal/day; $P>0.05$). The DLW TDEE was correlated with both FFM (r^2 = 0.89, $P<0.01$, power = 0.95) and total body weight (r^2 = 0.95, $P<0.01$, power = 0.99), whereas I-B TDEE was correlated only with total weight (r^2 = 0.75, $P<0.03$, power = 0.81). Under adverse field conditions the DLW method provided individual TDEE estimates that were probably more accurate than those provided by the I-B method.

108. Huff RL, JH Lawrence, WE Siri, LR Wasserman and TG Hennessy.
Effects of changes in altitude on hematopoietic activity.
Medicine 30:197-217, 1951.

Authors' Abstract

Three different groups of subjects in Lima (near sea level) and at Morococha (14,900 ft.), Peru were studied with regard to the usual physical and hematologic qualities as well as radio phosphorus blood volumes and radio iron turnover rates. One group of subjects was normal medical students of the University of San Marcos who were studied in Lima, and were then moved to Morococha where the studies were repeated as a function of time of stay there. The second group was normal natives of Morococha who were studied there and were then taken to Lima where the examinations were repeated after various intervals of time. The third group was abnormal natives of Morococha. The results of all of the usual studies were found to conform with previous similar investigations by other individuals. When the medical students moved to high altitude, there was a definite decrease in blood volume, primarily as a result of decreased plasma volume. The possible slight increase in red cell mass in the group during the 10-day period of acclimatization was within the limits of error of the measurements. The iron turnover rates increased by a factor of 2 with residence at 14,900 ft. Calculations show that the measured increases in red cell masses appearing after time at altitude are compatible with the observed production rate. It is observed that data on increases in red cell mass covering longer periods of acclimatization at Morococha fit an increase in production rate of a factor of 2. However, the value is too high to give an eventual increase in red cell mass that would be comparable to that of the natives of Morococha. Therefore, it is suggested that a decrease in this rate probably occurs with longer periods of acclimatization, since the ratio of red cell volume of the native at altitude to the student at sea level is 1.51. When the natives moved to Lima there was little change in blood volume but approximately a 10 per cent decrease in red cell mass in 10 days of observation. The iron turnover rates fell linearly with time to approximately 0.1 the original value in 10 days-values as low as those seen in patients with aplastic anemia. Calculations show that about one-half the decrease in red cell mass is the result of a decreased production rate and that the other half may be the result of an increased rate of destruction. This decrease in production rate is not compatible with life if extended over a longer period of time. Thus during the period greater than 10 days the rate must return to more nearly normal for sea level dwellers.

The abnormal natives with silicosis at Morococha had very high red cell masses and decreased plasma volumes. The iron turnover rates were excessively high. The rate constants were as great as those seen in the most severe polycythemia vera cases (6). The per cent of red cell iron renewed per day was greater than in the normal natives of Morococha.

109. Humpeler E, F Skrabal and G Bartsch.
Influence of exposure to moderate altitude on the plasma concentration of cortisol, aldosterone, renin, testosterone, and gonadotropins.
European Journal of Applied Physiology 45:167-176, 1980.

Authors' Abstract

The influence of 11 days at moderate altitude (2,000 m) combined with exercise on plasma concentration of testosterone, FSH (follicle-stimulating hormone), LH (luteinizing hormone), cortisol, aldosterone, and renin activity was studied in ten healthy subjects. Within 48 h of arrival at moderate altitude a significant increase in testosterone was found, whereas FSH had decreased significantly and LH showed a tendency to decrease. Cortisol increased significantly at the beginning and reached a maximum at the end of altitude exposure. The plasma aldosterone level rose continuously and on the last day of altitude was significantly elevated. Plasma renin activity showed a tendency to decrease. On return to low land all measured parameters returned to base line values within 2 days.

The findings of increases in plasma levels of aldosterone and testosterone (and serum T_3 and T_4, as reported by others) are in contrast to the previously found decrease of urinary excretion of all these hormones. This appears to be a distinct dissociation of serum levels of adrenal (and thyroid) hormones from their urinary excretion.

The observed increase in plasma aldosterone is probably mediated through ACTH and the rise in plasma potassium, since plasma renin activity showed an opposite trend. The rise in plasma testosterone is probably of adrenal origin since plasma gonadotropins declined simultaneously.

The increase of plasma levels of glucocorticoids, mineralocorticoids, and androgens after an ascent from 600 m to 2,000 m above sea level is compatible with an ACTH-mediated stimulation of the entire adrenal cortex and/or a diminished elimination of adrenal steroids: The concomitant fall of FSH, LH, and plasma renin would then be a consequence of a direct negative feedback inhibition of these hormones.

110. Hurtado A.
Studies at high altitude: blood observations on the Indian Natives of the Peruvian Andes.
American Journal of Physiology 100:487-505, 1932.

Authors' Abstract

A number of observations on certain of the blood characteristics of the Indian natives of the Peruvian Andes have been presented in this work. The investigation has been conducted in the town of Morococha, Peru, at an altitude of 14,890 feet, and with an average barometric pressure of 410 mm Hg. The subjects studied have been carefully selected as normal men, and the results obtained suggest the following conclusions:

1. Observations on the erythrocyte count gave an average increase of about a million red cells per cubic millimeter over the sea level normal value, but a considerable percentage of these natives live with a red cell count which would be considered normal at sea level. This finding indicates that an increase in the erythrocytes of the circulating blood, although the common finding, is not an essential adaptation process for normal life at high altitudes. There is no relationship between the red cell count and age or body measurements.

2. The average number of grams of hemoglobin per 100 cc. of blood has almost the same value as the normal average at sea level. In only 50 per cent of the cases was a higher result obtained.

Each red cell at high altitude contains less hemoglobin, as compared with the normal erythrocyte at sea level, but the corpuscular hemoglobin is not a fixed characteristic: it varies inversely with the level of the red cell count, that is, the higher the count the less hemoglobin in each cell and vice versa.

Oxygen determinations in arterial and venous blood verify these findings, and indicate that the red cell comes to the tissues

with a lower oxygen content as compared with the erythrocyte at sea level.

3. There is a marked increase in the hematocrit (RBC per cent), and it is proportionally greater than the increase in the red cell count, with the result that each erythrocyte has a larger volume (as compared with the normal corpuscle at sea level). Again the corpuscular volume is not a fixed characteristic: it varies inversely with the level of the red cell count.

The larger size of the erythrocytes has also been confirmed by direct measurement of it's diameter.

4. The diminished amount of hemoglobin in a larger corpuscle gives a lower value for the concentration of that substance in relation to the volume of the cell. Only about one-fourth of the erythrocyte is saturated with hemoglobin. Equal and parallel changes in cell volume and hemoglobin, under the influence of variations in the red cell count, keep remarkably constant such concentration.

There is an almost perfect inverse correlation between the hematocrit (RBC per cent) and the hemoglobin concentration in each red cell.

5. The above findings suggest that the adaptation processes to the high altitude, from the point of view of blood morphology, are to be found not primarily in red cell count and hemoglobin increases, as it has often been remarked, but rather in a fine and close correlation between cell number, volume and hemoglobin, and in the existence of a larger surface area in a given volume of blood and in the individual erythrocyte for the hemoglobin and oxygen content, factors which would favour the proper supply of this gas to the tissues, this last process being perhaps the basic and fundamental problem at high altitude.

6. The viscosity of the blood is definitely increased, whereas that of the plasma and serum remains strictly normal.

7. The red cells show a marked increase in the resistance to hemolysis. This is most likely related to the presence of young erythrocytes produced by the overactive bone marrow.

8. A positive indirect Van den Bergh reaction was obtained in most cases examined, and actual determinations of the plasma bilirubin gave results slightly above normal. This finding may be related to an increased rate of cell destruction, perhaps a compensatory process to balance the increased formation of red cells.

9. The blood coagulation time has a slight tendency to be shortened at high altitude. It has some inverse relation to the degree of the blood viscosity.

10. The average leucocyte count in these natives is essentially normal, but with a tendency to be low.

11. The average leucocytic formula falls within normal percentages of sea level values, with the exception of a decrease in the eosinophiles. Not infrequently a relative polynucleosis and monocytosis is found.

Young polynuclear cells are frequently observed. In a considerable number of cases histiocytes are found in the peripheral blood, indicating perhaps an overactivity of the reticulo-endothelial system.

111. Hurtado A, C Merino and E Delgado.
Influence of anoxemia on the hemopoietic activity.
Archives of Internal Medicine
75:284-323, 1945.

Authors' Abstract

Investigations have been made at sea level and at high altitudes, in several series of healthy and diseased male subjects, concerning the influence of temporary, intermittent and chronic anoxic anoxia (anoxemia) on the morphologic and other characteristics of the circulating blood. The related literature has been briefly reviewed. The main observations lead to the following conclusions:

1. Exposure to a low barometric pressure environment causes in most cases a polycythemic response. There are wide individual variations, but in general the level of polycythemia is directly proportional to the degree, duration and continuity of the anoxic stimulus.

2. There seems to be a limit for the hematologic response to the anoxic stimulus. When this is extremely severe, a decrease rather than a further increase, is observed in the resulting polycythemia. An interference with the formation of hemoglobin may be the responsible mechanism.

3. The level of hemoglobin in the circulating blood may be considered as one of the many factors which tend to preserve the internal stability, or homeostasis, against the

disturbing influence of a constant lowering of the oxygen tension in the inspired air.

4. The polycythemia associated with the anoxemia of high altitudes is absolute in type. The elevation in the total blood volume, which at times reaches high values, is due to an increased red cell volume.

5. The polycythemia observed on persons' arrival at high altitudes seems to be due to factors of release of stored blood and hemoconcentration; that corresponding to a repeated or constant exposure to a low pressure environment is related to an erythropoietic hyperactivity.

6. The polycythemia associated with a constant or intermittent anoxemia tends to show a proportional elevation in the circulating reticulocytes and in the serum bilirubin. The latter characteristic suggests that an increased rate of cellular destruction parallels the increased formation, but other factors such as insufficiency of the liver in excretion of pigment, due to the anoxic condition, may also play an etiologic role in the observed hyperbilirubinemia.

7. The stimulating influence of anoxemia on the hemopoietic system is restricted to the formation of red blood cells and hemoglobin. Leukopoietic activity is not affected, and the moderate and temporary leukocytosis which at times is observed on a person's arrival at a high altitude is probably related to the release and mobilization of stored blood.

8. Chronic anoxemia does not modify the erythropoietic activity permanently. When a person who has lived since birth at high altitudes is brought down to sea level, he shows after some time blood characteristics similar to those found in persons who have always lived under the latter environmental conditions. During the early period of adaptation to the normal pressure environment there frequently occurs an abnormal decrease in the red blood cells and hemoglobin.

9. Comparative study of the polycythemia of high altitudes and the polycythemic processes observed at sea level indicates that: (a) in cases of anoxemia at sea level due to pulmonary changes, the polycythemic response tends to be less than with corresponding degrees of arterial oxygen unsaturation at high altitudes, except in cases of Ayerza's disease; (b) it is not likely that the causative mechanism of polycythemia vera is related to the existence of an anoxic stimulus.

112. Hyers TM, CH Scoggin, DH Will, RF Grover and JT Reeves.
Accentuated hypoxemia at high altitude in subjects susceptible to high-altitude pulmonary edema.
Journal of Applied Physiology 46:41-45, 1979.

Authors' Abstract

To investigate the hypotheses that activated coagulation, catecholamine release, or arginine vasopressin release are involved in the pathogenesis of high-altitude pulmonary edema (HAPE), we measured these variables in seven subjects susceptible to HAPE and in nine control subjects at an alitutde of 1,600 m and after 6 and 12 h at a simulated altitude of 4,150 m. Each subject was studied twice, once after 3 days of placebo medication and once after 3 days of premedication with aspirin and dipyridamole. At high altitude, HAPE-susceptible subjects showed significantly exaggerated hypoxemia and a slightly higher end-tidal carbon dioxide partial pressure that did not account fully for the hypoxemia. Fibrinolytic activity was significantly accelerated in both groups at high altitude, whereas other coagulation measurements, catecholamines and arginine vasopressin levels, and pulmonary function tests were not significantly changed. Similar findings were obtained after both placebo and platelet inhibitor premedication. The results indicate that none of the three hypothesized mechanisms, i.e., activated coagulation, excessive catecholamine release, or antidiuresis, would account for HAPE susceptibility. Instead, HAPE-susceptible subjects exhibited exaggerated hypoxemia associated with relative hypoventilation and a widened alveolar-arterial gas pressure difference.

113. Jain SC, J Bardhan, YV Swamy, A Grover and HS Nayar.
Body water metabolism in high altitude natives during and after a stay at sea level.
International Journal of Biometeorology 25:47-52, 1981.

Authors' Abstract

Body fluid compartments were studied in a group of high altitude natives after a stay of two months at sea level and during 12 days at an altitude of 3,500 m. Measurements of total body water and extracellular water were made on day 3 and 12 of reinduction to altitude, while plasma volume was measured on day 12 only. The intracellular water, blood volume and red cell mass were computed from the above parameters. Total body water and intracellular water decreased by 3.3% (P<0.001) and 5.0% (P<0.001), respectively, by the 3rd day at altitude and did not change thereafter. Extracellular water increased progressively at altitude, but the increase was not significant. Blood volume and red cell mass increased significantly while plasma volume decreased at altitude. These data were compared with those of low landers. This study suggested body hypohydration on high altitude induction in low landers as well as in high altitude natives on reinduction.

114. Jain SC, J Bardhan, YV Swamy, B Krishna and HS Nayar.

Body fluid compartments in humans during acute high-altitude exposure.

Aviation, Space, and Environmental Medicine 51:234-236, 1980.

Authors' Abstract

Body fluid compartments were studied in a group of sea level residents at sea level and during 12 d of acute exposure to an altitude of 3,500 m. Measurements of total body water and extracellular water were done on the third and 12th days of exposure, while plasma volume was measured on 12th day only. The intracellular water, blood volume, and red cell mass were computed from the above parameters. Total body water and extracellular water decreased progressively, the decrease being 4.7% (p<0.001) and 6.0% (p<0.05), respectively, on the 12th day. Plasma volume and blood volume decreased significantly with a slight increase in red cell mass. Intracellular water, computed from total body water and extracellular water, decreased by 4.3% on 12th day. This study suggested hypohydration on acute altitude exposures.

115. Jain S, WL Wilke and A Tucker.

Age-dependent effects of chronic hypoxia on renin-angiotensin and urinary excretions.

Journal of Applied Physiology 69:141-146, 1990.

Authors' Abstract

The mechanisms regulating water, electrolyte, and blood volume homeostasis continue to mature in early postnatal life, and this maturation may be altered by perturbations of volume or cardiovascular status. To evaluate the long-term effects of chronic hypoxia on water balance, urinary electrolyte excretion, heart weights, systemic arterial pressure, and components of the renin-angiotensin system, male Sprague-Dawley rats were exposed to periods of simulated altitude of 10,000 ft up to 90 days of age beginning at 2 or 30 days of age. Altitude exposure of both neonatal and adult rats was associated with increases in urine output and water intake after 30 days of exposure, and right ventricular (RV) hypertrophy at all ages was examined. However, the percent increase in urine output, water intake, and RV hypertrophy was numerically greater in neonates. Neonates also had increases in urinary sodium and potassium excretion after 30 days of exposure. Plasma renin activity and serum angiotensin-converting enzyme (ACE) activity were not affected, but plasma renin substrate was reduced in both neonatal and adult altitude-exposed rats. Lung ACE activity was also decreased in altitude-exposed neonates. These data indicate that the degree and, in some cases, the nature of these homeostatic responses varies with age during long-term hypoxia.

116. Janoski AH, BK Whitten, JL Shields and JP Hannon.

Electrolyte patterns and regulation in man during acute exposure to high altitude.

Federation Proceedings 28:1185-1189, 1969.

Authors' Abstract

Ten male volunteers in their early twenties were maintained on a constant sodium and potassium intake for 14 days at sea level, the day of transition, and 9 days at high altitude (14,100 ft) to determine the effects of prolonged hypoxia on water and electrolyte

regulation. Decreased urine volume occurred at high altitude and was correlated with diminished water intake. Urinary potassium retention was observed and serum potassium increased. There were no significant changes in urinary or serum sodium concentrations. The findings are discussed in light of reports demonstrating decreased aldosterone secretion at high altitude.

117. Jezek V, A Ourednik, S Daum and L Krouzková.
Effect of short-term hypoxaemia on the potassium and sodium metabolism and on cardiac contraction.
Acta Medica Scandinavica 177:175-182, 1965.

Authors' Abstract

In a group of 12 healthy subjects and 11 patients with chronic cor pulmonale, a short-term reduction in the oxygen saturation of arterial blood was induced by inhalation of a gas mixture with a low oxygen content. Values in the course of cardiac contraction, the plasma sodium, plasma potassium and red-cell levels were investigated as well as the urinary sodium and potassium excretions.

In both examined groups, already during hyposaturation there develops a marked increase of the plasma potassium levels and a reduction of the red-cell potassium content. The changes persist for one hour after the termination of hyposaturation and initial values are reached within 24 hours. In patients with chronic cor pulmonale, an increased urinary potassium excretion was observed during the period immedicately after the induced hyposaturation. In healthy subjects the potassium excretion does not differ from the normal diurnal cycle. In neither of the two groups were changes found in the plasma sodium levels or the urinary sodium excretion.

In patients with cor pulmonale, prolongation of isometric contraction during hypoxaemia as an index of the loss of contractility of myocardium was found. In healthy subjects these changes did not occur.

The mechanism of the described changes is discussed.

118. Johnson HL, CF Consolazio, LO Matoush and HJ Krzywicki.
Nitrogen and mineral metabolism at altitude.
Federation Proceedings 28:1195-1198, 1969.

Authors' Abstract

Nitrogen balances of 15 men receiving two different liquid diets were positive at sea level and negative at altitude but appeared to be partially a reflection of intake of both nitrogen and calories since dietary intake was greatly reduced at altitude. Sodium balances, exclusive of sweat losses, were positive at sea level and negative at altitude while potassium was retained at sea level and balances near equilibrium were observed at altitude. Calcium losses, attributed to low intakes, were observed throughout the study and magnesium balances were generally positive. Large weight losses during the 1st days on the diet and again at altitude indicated body water losses. Weight gains upon return to sea level were attributed to water retention.

119. Jung RC, DB Dill, R Horton and SM Horvath.
Effects of age on plasma aldosterone levels and hemoconcentration at altitude.
Journal of Applied Physiology 31:593-597, 1971.

Authors' Abstract

Total blood volume, red cell and plasma volume, and plasma aldosterone levels were measured on a group of four young and four older subjects at sea level and altitude. Red cell volumes were unchanged; however, there was a reduction in plasma volume in both groups with the young subjects showing a slightly greater reduction. Plasma aldosterone levels were reduced in the older subjects but remained at sea-level or higher values in the younger subjects upon ascent to altitude. It is concluded that plasma aldosterone levels and, therefore, probably secretion rates may be affected by age and that plasma volume may be similarly affected by age. The changes in these values at altitude appear to be delayed in physiologically older individuals. Possible mechanisms for this discrepancy with age are discussed. It is suggested that caution should be used in analyses and interpretation of body fluid changes and hormonal secretory values at altitude unless these are age correlated and plasma hormone levels analyzed rather than using urine excretory concentrations.

120. Kawashima A, K Kubo, K Hirai, S Yoshikawa, Y Matsuzawa and T Kobayashi.
Plasma levels of atrial natriuretic peptide under acute hypoxia in normal
Respiration Physiology 76:79-92, 1989.

Authors' Abstract

To investigate whether the acute hypoxia can be a stimulus for atrial natriuretic peptide (ANP) secretion, plasma levels of ANP were determined under three different hypoxic conditions in six normal subjects. During 15% O_2 breathing for 10 min, no significant change in plasma ANP level was observed. Severe hypoxia induced by 10% O_2 breathing increased the mean pulmonary arterial pressure (P_{pa}) by 11.6 mm Hg within 10 min ($P<0.01$), accompanying a slight but significant rise in plasma ANP level of pulmonary artery (PA) from 24.3 ±5.3 to 28.2 ±4.6 pg/ml ($P<0.05$). There was a tendency for the ANP level of PA to rise under hypoxic hypobaria at 515 Torr for 10 min, followed by a decrease of that level during 100% O_2 breathing under hypobaric conditions. These changes, however, still remained in the normal range. No significant changes were observed both in right atrial pressure and in pulmonary capillary wedge pressure under any of the three hypoxic conditions. From these results we conclude that ANP can be released in response to the elevation of P_{pa} caused by acute hypoxia in normal subjects, but the changes in plasma ANP level may be too small to play a significant physiological role in hemodynamic responses to acute hypoxia.

121. Kawashima A, K Kubo, Y Matsuzawa, T Kobayashi and M Sekiguchi.
Hypoxia-induced ANP secretion in subjects susceptible to high-altitude pulmonary edema.
Respiration Physiology 89:309-317, 1992.

Authors' Abstract

We investigated the effects of acute hypoxia (10% O_2) on plasma level of atrial natriuretic peptide (ANP) and pulmonary hemodynamics in five subjects with a history of high-altitude pulmonary edema (HAPE). Plasma renin activity and plasma levels of aldosterone, epinephrine and norepinephrine were also measured. The plasma ANP levels in HAPE-susceptible subjects rose significantly in response to 10% O_2 (from 34.8 ±5.4 to 51.4 ±7.3 $pg \cdot ml^{-1}$; $P<0.05$), not associated with any increase in either atrial pressure. Compared with six control subjects, the rise of ANP level was greater in HAPE-susceptible subjects (16.6 ±4.4 vs 3.9 ±1.2 $pg \cdot ml^{-1}$; $P<0.05$). There was a significant positive correlation between the rise of ANP level and the increase of pulmonary arterial pressure. No significant difference was observed in any of other hormonal responses to acute hypoxia between the two groups. We interpret these results as indicating that the ANP secretory response to acute hypoxia in HAPE-susceptible subjects, which is not mediated by an increase in arterial pressure, may be greater than that in nonsusceptible subjects in association with a greater pressor response of pulmonary circulation.

122. Keynes RJ, GW Smith, JDH Slater, MM Brown, SE Brown, NN Payne, TP Jowett and CC Monge.
Renin and aldosterone at high altitude in man.
Journal of Endocrinology 92:131-140, 1982.

Authors' Abstract

Measurements have been made of hormonal changes relevant to salt and water balance during prolonged exposure to hypoxia to improve our understanding of the syndrome of acute mountain sickness. We have attempted to delineate the detailed inter-relationships between the renin-aldosterone and the vasopressin systems by a metabolically controlled study, involving an orthostatic stress (45^0 head-up tilt) and an injection of a standard dose of ACTH to test adrenal responsiveness. Three Caucasian medical students underwent a 7-day equilibration at 150 m (Lima, Peru), followed by a 6-day sojourn at 4350 m (Cerro de Pasco, Peru) and a final 7 days at 150 m. Measurements were made of sodium and potassium balance, body weight, and the 24-h renal excretion of vasopressin, cortisol and

aldosterone 18-glucuronide. These variables showed little change, except for that of aldosterone 18-glucuronide, which fell sharply at altitude and rebounded even more sharply on return to sea level. At altitude, basal plasma levels of renin activity and aldosterone fell, and the response to orthostasis was attenuated, but the fall of plasma renin activity, as compared to plasma aldosterone, was delayed; on return to sea level this dissociation was exacerbated with the return of normal renin responsiveness lagging behind that of aldosterone. We suggest that unknown factors which dissociate the orthodox renin-aldosterone relationship, other than the activity of the angiotensin I-converting enzyme, are operative on exposure to hypoxia.

123. Kjeldsen K and F Damgaard.
Influence of prolonged carbon monoxide exposure and high altitude on the composition of blood and urine in man.
Scandinavian Journal of Clinical and Laboratory Investigation 103:20-25, 1968.

Authors' Abstract

The influence of exposure to carbon monoxide (average carboxyhaemoglobin saturation 13 per cent) and high altitude (3,454 m) on a number of compounds in blood and urine was investigated in 8 healthy volunteers for 8 and 10 days, respectively. Reticulocyte counts increased 2-3 fold; moderate increases were seen in the urinary volume, on an average 400-800 ml/24 hrs. Compared to the remaining days of the study, significantly higher amounts of sodium, chloride and calcium were excreted on the first day of exposure to both forms of hypoxia.

124. Klain GJ and JP Hannon.
Effects of high altitude on lipid components of human serum.
Proceedings of the Society of Experimental Biology and Medicine 129:646-649, 1968.

Authors' Abstract

Serum lipid components were measured in eight male subjects exposed to an altitude of 14,000 feet for 14 days. Concentrations of total lipids rapidly decreased after the third day of exposure and a similar, although less pronounced, decrease was observed in cholesterol levels. By way of contrast, phospholipid and FFA levels progressively increased during the period of altitude exposure. High altitude had no effect on serum glucose concentration, but caused a slight increase in serum water content. The data indicate that high altitude has a marked effect on lipid metabolism.

125. Klausen T, T Mohr, U Ghisler and OJ Nielsen.
Maximal oxygen uptake and erythropoietic responses after training at moderate altitude.
European Journal of Applied Physiology 62:376-379, 1991.

Authors' Abstract

Six well-trained male cross-country skiers trained for 7 days at 2700 m above sea level, their accommodation being at 1695 m. Blood samples for haemoglobin concentration [Hb], erythropoietin concentration [EPO] and reticulocyte count were collected before, during and after altitude exposure. Packed cell volume (PCV), red blood cell count (RBC), transferrin-iron saturation, mean red cell volume (MCV), mean corpuscular haemoglobin concentration (MCHC), maximal oxygen uptake, maximal achieved ventilation and heart rate were determined pre- and post-altitude exposure. The [EPO] increased significantly from pre-altitude (mean 36 $mU \cdot ml^{-1}$, SD 5) to maximal altitude values (mean 47 $mU \cdot ml^{-1}$, SD 3). The [Hb] had increased significantly above pre-altitude values (mean 8.8 $mmol \cdot l^{-1}$, SD 0.5) on day 2 (mean 9.1 $mmol \cdot l^{-1}$, SD 0.4) and day 7 (mean 9.4 $mmol \cdot l^{-1}$, SD 0.4) at altitude and on day 4 post-altitude (mean 9.2 $mmol \cdot l^{-1}$, SD 0.4). The reticulocyte counts had increased significantly above pre-altitude values (mean 6%, SD 3%) on day 3 at altitude (mean 12%, SD 8%) and day 4 post-altitude (mean 10%, SD 5%). The RBC counts had increased on the 4th post-altitude day. The transferrin-iron saturation had decreased below pre-altitude values (mean 23%, SD 4%) on day 4 post-altitude (mean 14%, SD 5%) and had increased on day 11 post-altitude (mean 22%, SD 7%). There were no significant changes in MCV, MCHC, PCV, maximal oxygen uptake and maximal achieved ventilation, and heart rate pre- to post-altitude. These observations demonstrated an erythropoietic response to the altitude training which was not sufficient to increase the post-altitude maximal oxygen uptake.

126. Klausen K, B Rasmussen, H Gjellerod, H Madsen and E Petersen.
Circulation, metabolism and ventilation during prolonged exposure to carbon monoxide and to high altitude.
Scandinavian Journal of Clinical and Laboratory Investigation 103:26-38, 1968.

Authors' Abstract

Eight male subjects were investigated at rest and work during normal sea level conditions (control) and the results were compared with experiments performed during prolonged exposure to two different hypoxic conditions of the same magnitude: 1) Anemic hypoxia (carbon monoxide poisoning) and 2) hypoxic hypoxia (3454 m above sea level). Almost no change of circulation, metabolism and ventilation was seen during anemic hypoxia. The changes found during hypoxic hypoxia confirm previous investigations by others. From the results it was calculated that the mean oxygen tension in the tissues during rest was decreased during anemic hypoxia by about 15-20 per cent as compared to the control values, while it was unchanged during hypoxic hypoxia. It is concluded that the regulatory functions of the organism during prolonged exposure to hypoxia respond to a decrease of the arterial oxygen tension.

127. Koller EA, A Bührer, L Felder, M Schopen and MB Vallotton.
Altitude diuresis: endocrine and renal responses to acute hypoxia of acclimatized and non-acclimatized subjects.
European Journal of Applied Physiology 62:228-234, 1991.

Authors' Abstract

As a result of our recently published studies we have thought that altitude diuresis resulting from hypoxic stimulation of the arterial chemoreceptors reduces the cardiac volume overload. To test this hypothesis, cardiovascular, endocrine and renal responses to stepwise acute exposure to simulated altitude (6,000 m) were compared in ten acclimatized recumbent mountaineers a mean of 24 days, SD 11, after descending from Himalayan altitudes of at least 4,000 m, with those found in ten non-acclimatized recumbent volunteers. The results showed that natriuresis and diuresis typified the renal responses to altitude exposure of both the acclimatized as well as non-acclimatized subjects, as long as altitude was well tolerated. It was concluded that the renal effects were mediated by atrial natriuretic peptide release and slight suppression of arginine-vasopressin (AVP) secretion, that the increased urine flow at altitude offset the cardiac (volume) overload resulting from hypoxic stimulation of the arterial chemorecoptors, and that enhanced AVP secretion, as found in the non-acclimatized subjects at and above 4,000 m, coincided with subjective and objective distress; i.e., with inadequate altitude adjustment owing to insufficient chemoreflex effects and central hypoxia.

128. Koller EA, M Schopen, M Keller, RE Lang and MB Vallotton.
Ventilatory, circulatory, endocrine, and renal effects of almitrine infusion in man: a contribution to high altitude physiology.
European Journal of Applied Physiology 58:419-425, 1989.

Authors' Abstract

Diuresis at altitude was thought to be the result of chemoreceptor stimulation leading to a reduction of cardiac volume overload. This hypothesis was tested in ten young, healthy subjects by infusion of almitrine ($0.5 \text{ mg} \cdot \text{kg}^{-1}$ body mass within 30 min) assuming analogous sites of action; i.e., arterial chemoreceptors and pulmonary vessels, for almitrine as for hypoxic hypoxia. The results show that almitrine increases ventilation, heart rate, systolic blood pressure, central venous pressure, and natriuresis, but fails to increase significantly atrial natriuretic peptide plasma concentration and diuresis. It is concluded: (1) that almitrine has similar sites of action as hypoxic hypoxia at about 5000 m, (2) that natriuresis during arterial chemoreceptor stimulation might reduce cardiac volume overload, (3) that the volume excretion hypothesis, in particular the pathways from the cardiac volume overload to the water

diuresis, need, for an understanding of the hypoxia-induced diuresis, further direct investigations at altitude.

129. Korol’kov VI, MA Dotsenko, AI Grigor’ev and GI Kozyrevskaya. Water and mineral metabolism and kidney function in man at high altitudes. *Fiziologiya Cheloveka* 50:849-854, 1979.

Annotation

Purpose

To study water and mineral metabolism and the state of kidney function during gradual acclimatization of man to high altitudes.

Methods

Observations were made on six healthy men (aged 18-25 yr) with same standard of training and same resistance to hypoxia by working up to their limit of tolerance on a bicycle ergometer in a pressure chamber during “ascent” to an altitude of 5,000 m with a 30-min exposure. After two background observations, subjects were taken to an altitude of 2200 m for 12 days and then to 3200 m for 12 days; their motor activity was unrestricted after descent from mountains when they were monitored for 9 days. Subjects were fed a standard diet of natural products of 3000 kcal/day during the entire investigation.

Determinations were made of body weight, and serum and urine concentrations of sodium, potassium and osmolality. On the 9th day at 2200 and 3200 m, arterial gas composition and acid-base balance was determined. Hemotocrit, plasma volume, serum and urine creatinine levels, and renal plasma flow were determined on the subjects at 3200 m. Blood volume, packed cell volume, glomerular filtration rate, resistance to blood flow in the kidneys, osmotic index and osmotic clearance of water were calculated.

Results

At 2200 m fluid intake was unchanged, but at 3200 m it was at the initial level and remained so during the ten days of recovery. Diuresis at 3200 m averaged 280 ml above its initial level. The excess of water intake over volume of urine excreted was reduced by 22% at 2200 m and by 82% at 3200 m. Renal loss of fluid during the training period was 64%; whereas at 2200 m and 3200 m it was 71% and 92%, respectively. This higher loss may be the result of a combination of hypoxia and low air temperature. The rate of excretion of osmotically free water was increased and, at its height, the osmolarity of the urine decreased from 76 to 54 milliosmols/liter. The osmotic index and osmotic concentration of the blood were unchanged. There was an increase in renal excretion of sodium, but not for potassium. Arterial blood pH at 3200 m increased from 7.40 to 7.43; the true carbonate was reduced from 24.9 to 22.6, and the total CO_2 concentration was reduced from 26.2 to 23.6, and the P_{CO_2} decreased from 42 to 33 mm Hg. Although there were increases in circulating blood volume and hematocrit, there was no change in renal plasma flow.

Conclusions

In healthy subjects at high altitudes with no restriction on movements, exposure to hypoxia and low air temperature leads to increased renal excretion of water and decrease in water intake. The rate of excretion of osmotically active substances and sodium is increased, especially at 3200 m. The rate of glomerular filtration and renal plasma flow are not affected, but there are increases in circulating blood and packed cell volumes. The changes in the osmo-and ion-regulatory function of the kidneys could probably be ascribed to changes in the hemodynamics or to neuroendocrine mechanisms of regulation of water and electrolyte homeostasis. The absence of hypohydration may be the result of graded acclimatization which promotes more adequate adaptive reactions of the body to hypoxia.

130. Kotchen TA, RP Hogan, AE Boyd, T-K Li, HC Sing and JW Mason. Renin, noradrenaline and adrenaline responses to simulated altitude. *Clinical Science* 44:243-251, 1973.

Authors’ Abstract

1. Plasma renin activity, plasma adrenaline and noradrenaline concentrations, and urinary adrenaline and noradrenaline excretion rates were measured in ten subjects during 3 days of exposure to a simulated altitude of 12,000 ft.

2. In both the supine and standing positions, renin activities were suppressed during all 3 days at altitude.

3. Plasma noradrenaline and adrenaline concentrations were significantly increased by the third day at altitude.

4. Urinary adrenaline excretion tended to be increased during the entire 3 days at altitude, with no significant change between the first and third day. Noradrenaline excretion was significantly increased on the third day.

5. The finding of decreased renin levels suggests that the enhanced activity of the sympathetic nervous system at high altitude does not stimulate renin release.

131. Krzywicki HJ, CF Consolazio, HL Johnson, WC Nielsen Jr and RA Barnhart.

Water metabolism in humans during acute high-altitude exposure (4,300 m).

Journal of Applied Physiology 30:806-809, 1971.

Authors' Abstract

During 6 days of altitude exposure at 4,300 m, the following changes in body water compartments were observed. a) Total body water was significantly decreased by 2.25 kg during the 6-day altitude exposure. b) Extracellular water appeared to increase by 1.27 kg at altitude, although not significantly. c) Intracellular water, in turn, was significantly decreased by 3.52 kg at altitude, which is contrary to some previous reports. Under the conditions of this study, with heavy physical activity prior to and during altitude exposure, and with fairly high food intakes (above 3,400 kcal/day), it appeared that hypohydration and a diuresis still occurred during acute altitude exposure. This suggested that body water loss may have been an adaptive mechanism in acute altitude exposure.

132. Krzywicki HJ, CF Consolazio, LO Matoush, HL Johnson and RA Barnhart.

Body composition changes during exposure to altitude.

Federation Proceedings 28:1190-1194, 1969.

Authors' Abstract

Body composition was studied in two groups of men fed liquid diets for 8 days at sea level, 12 days after abrupt exposure to high altitude (4,300 m), and 7 days of sea level rehabilitation. One group was fed a 3,600 kcal liquid diet with 48% of the Calories as carbohydrate and 40% as fat. The second group was fed a high carbohydrate-low fat diet (68 and 20% of the Calories, respectively). Significant body weight change at altitude of 3.54 and 3.96 kg in groups I and II which were partitioned into significant losses of 1.29 and 1.46 kg of fat, 1.77 and 1.85 kg of body water, 0.32 and 0.47 kg of body protein, and 0.16 and 0.18 kg of mineral, respectively. Body weight lost in excess of that attributable to the caloric deficit appeared to be due to a loss of body water. Blood and plasma volumes demonstrated significant decreases at altitude, which also seem to indicate hypohydration of the body.

133. Lawless JJ and EJ Van Liere.

The effect of various degrees of anoxic anoxia on water distribution in the body.

American Journal of Physiology 149:103-106, 1947.

Annotation

Purpose

To study the effect of short periods of various degrees of anoxic anoxia on the water content of different tissues of animals.

Methods

Male Wistar albino rats of 110-150 days were used. Paired animals were weighed; one placed in the low-pressure chamber and the other (control) kept in an adjacent cage for 3 ½ hours. The low-pressure corresponded to altitudes of 8,000, 18,000, and 28,000 ft. No food or water was permitted to the animals during the experiment. At the end of the experiment the animals were weighed and the water content of the liver, adrenals, cerebellum, abdominis rectus and quadratus, skin from the back and abdomen, and kidney was determined.

Results

Animals subjected to various degrees of anoxic anoxia for a period of 3 ½ hours showed no significant changes in water content of several important tissues. The data for the adrenal glands were inconclusive. The water content of muscles and skin was indeterminate; in some cases the amount of water was increased and in others decreased. The cerebellum, kidney and liver showed no important changes in water content following anoxia. All the animals lost a significant amount of weight following a 3 ½ hour exposure to anoxic anoxia, even at the simulated altitude of 8,000 feet.

Conclusions

Since all animals exposed to anoxic anoxia lost a significant amount of body weight and the various organs studied did not show a significant loss of water, it was concluded that hemoconcentration took place. Thus, the body, to maintain its homeostatic state, allowed the blood (and probably the extracellular spaces) to lose water rather than the tissue cells. Furthermore, the inconstant results suggests that there was a threshold duration of anoxia.

134. Lawrence DL, JB Skatrud and Y Shenker.
Effect of hypoxia on atrial natriuretic factor and aldosterone regulation in humans.
American Journal of Physiology 258:E243-E248, 1990.

Authors' Abstract

To evaluate the possible physiological role of atrial natriuretic factor (ANF) on the observed dissociation of aldosterone from the renin-angiotensin system during acute hypoxia, 7 men, ages 18-27 yr, were studied on two separate days for 1 h under hypoxic (12% O_2) and normoxic (room air) conditions. Subjects were on a low-salt diet (urinary sodium 67 ±13 meq / 24 h) and suppressed with dexamethasone. Hemoglobin saturation decreased during hypoxemia to 68 ±1% ($P<0.01$), whereas heart rate increased from 65 ±3 to 89 ±5 beats/min ($P<0.01$). Plasma aldosterone levels decreased 43% from basal during hypoxemia ($P<0.01$), whereas ANF levels increased by 50% ($P<0.05$). Levels of both were unchanged during normoxemia. Plasma renin activity, angiotensin II, blood pressure, and pH did not change under either condition, and plasma cortisol levels were totally suppressed. These results indicate that acute hypoxemia is a potent stimulus for ANF release and that ANF is probably a major factor responsible for the dissociation of aldosterone from the renin-angiotensin system under these conditions.

135. Lawrence JH, RL Huff, W Siri, LR Wasserman and TG Hennessy.
A physiological study in the Peruvian Andes.
Acta Medica Scandinavica CXLII:117-131, 1952.

Authors' Abstract

1. The rise in red cell count and hematocrit developing in the early periods after ascent to altitude is due to hemoconcentration.
2. An increased or decreased rate in plasma iron turnover and subsequent incorporation of iron-59 in red cells measured with Fe^{59} is the most sensitive measure yet found for detection of change in the rate of hematopoietic activity.
3. A change in the rate of red cell production can explain the change in the number and volume of red cells resulting from variation in the oxygen in the inhaled air. It is not necessary to consider a change in the duration of life of the red cell as a mechanism of acclimatization.
4. In agreement with the findings of others, altitude polycythemia does not resemble polycythemia vera in that there is no concomitant enlargement of the spleen or thrombocytosis or leukocytosis.
5. There is no evidence for an increased incidence of polycythemia vera among the Peruvian Indians living at high altitude.
6. Ten days after descent from 14,900 feet to sea level, the iron turnover in the native Peruvian Indian decreased to one tenth that observed in his native habitat. This approaches that seen in aplastic anemia.

136. Leonard PJ, V Blackman and KW Jones.
Total body water, extracellular fluid, plasma volume and red cell mass in healthy East Africans.
Clinical Science 29:427-431, 1965.

Authors' Abstract

Kampala lies 830 miles inland from the east coast of Africa, 20 miles north of the equator at an altitude of 3900 ft above sea level. The air temperature fluctuates between 15^0C (60^0F) and 29^0C (85^0F). Variations in ambient temperature and altitude are known to affect the distribution of body fluids. Increases and decreases in temperature are associated with corresponding changes in the size of the plasma volume; and an increase in altitude results in an increased blood volume (Conley & Nickerson, 1945; Hurtado, Merino & Delgado, 1945; Doupe, Ferguson & Hildes, 1957).

Total body water, extracellular fluid, plasma volume and red cell mass were measured in healthy medical student volunteers so that local reference standards would be available.

1. Body spaces were measured in healthy male subjects living at an altitude of 3900 ft above sea level and exposed to a moderately high ambient temperature (15-29^{0}C; 60-85^{0}F) throughout the year.

2. Total body water was estimated using tritiated water, the extracellular fluid volume as the $^{35}SO_4$ space, and plasma volume by the ^{131}I-lablled human serum albumin technique in some subjects and by the ^{51}Cr technique in the remaining subjects.

3. Plasma volume was raised by at least 5 ml/kg in those studied.

4. Other results were within the usually accepted range of normal values.

137. Loeppky JA, RC Roach, MA Selland, P Scotto, FC Luft and UC Luft.

Body fluid alterations during head-down bed rest in men at moderate altitude.

Aviation, Space, and Environmental Medicine 64:265-274, 1993.

Authors' Abstract

To determine the effects of hypoxia on fluid balance responses to simulated zero-gravity, measurements were made in six subjects (acclimatized to 5,400 ft; 1,646 m) before and during -5^0 continuous head-down bed rest (HDBR) over 8 d at 10,678 ft. The same subjects were studied again at this altitude without HDBR as a control (CON) using a cross-over design. During this time, they maintained normal upright day-time activities, sleeping in the horizontal position at night. Fluid balance changes during HDBR in hypoxia were more pronounced than similar measurements previously reported from HDBR studies at sea level. Plasma volume loss (-19% on day 6) was slightly greater and the diuresis and natriuresis were doubled in magnitude as compared to previous studies in normoxia and sustained for 4 d during hypoxia. These changes were associated with an immediate, but transient, rise in plasma atrial natriuretic peptide (ANP) to day 4 of 140% in HDBR and 41% in CON ($p<0.005$), followed by a decline towards baseline. Differences were less striking between HDBR and CON for plasma antidiuretic hormone and aldosterone, which were transiently reduced by HDBR. Plasma catecholamines showed a similar pattern to ANP (+122%) in both HDBR and CON, suggesting that elevated ANP and catecholamines together accounted for the enhanced fluid shifts with HDBR during hypoxia.

138. Lozano R and C Monge C.

Renal function in high-altitude natives and in natives with chronic mountain sickness.

Journal of Applied Physiology 20:1026-1027, 1965.

Authors' Abstract

When compared with sea-level residents, the healthy natives living at an altitude of 4,540 m show a 12% reduction in the glomerular filtration rate, a 37% reduction in effective renal plasma flow, a 12% reduction in effective renal blood flow, and an increase of 39% in the filtration fraction. The corresponding values in patients with chronic mountain sickness living at 4,300 m above sea level are: glomerular filtration rate, 32% reduction; effective renal plasma flow, 57% reduction; effective renal blood flow, 9% increase; and filtration fraction, 56% increase. The mean hematocrit values of the healthy and sick natives investigated were 59 and 79%, respectively. The possible relationships between cardiac output, hematocrit values, and renal hemodynamics are discussed.

139. Lyons TP, SR Muza, PB Rock and A Cymerman.

The effect of altitude pre-acclimatization of acute mountain sickness during reexposure.

Aviation, Space, and Environmental Medicine 66:957-962, 1995.

Authors' Abstract

Acclimatization to high altitude appears to prevent acute mountain sickness (AMS), as evidenced by a decline in AMS symptoms as acclimatization progresses. We hypothesized that partial retention of acclimatization would

attenuate the incidence and/or severity of AMS upon reinduction to altitude. To test this hypothesis 6 male lowlanders returned to sea level after acclimatizing for 16 d at 4300 m (HA). After 8 d at sea level (PA), they were reexposed to 4300 m in a hypobaric chamber for 30 h (RA). AMS symptom severity was determined by the AMS-cerebral (AMS-C) scores calculated from the daily administration of the Environmental Symptoms Questionnaire during HA and RA. The mean AMS-C scores were reduced from 0.6 on HA day 1 (HA1) to 0.1 during RA ($p<0.05$). Four subjects were "sick" (AMS-C >0.7) during HA1, while only one was "sick" during RA. The % oxyhemoglobin, hemoglobin concentration and hematocrit were higher during RA compared to HA1. These results suggest that the retention of acclimatization after 8 d at low altitude is sufficient to attenuate AMS upon reinduction to high altitude.

140. Mackinnon PCB, ME Monk-Jones and K Fotherby.
A study of various indices of adrenocortical activity during 23 days at high altitude.
Journal of Endocrinology 26:555-566, 1963.

Authors' Abstract

1. Four men and three women ascended by télépherique and helicopter from 1000 to 4333 m. where they remained for 23 days.

2. Measurements of urinary 17-hydroxycorticosteroids, 17-oxosteroids, pregnanediol and pregnanetriol and circulating eosinophils were made at sea level and at high altitude.

3. An attempt was also made to measure changes in emotional activity by means of the palmar sweat index (PSI). This index was assessed at intervals throughout the day at sea level and at high altitude, and in response to adrenocorticotrophic hormone (ACTH) and a self-imposed stress.

4. Within 24 hr. of acute exposure to high altitude urinary 17-hydroxycorticosteroids increased whilst circulating eosinophils decreased; by the 5th day both were returning to sea-level values. The output of 17-oxosteroids was lower by the 5th day at high altitude and subsequently increased; pregnanediol and pregnanetriol levels remained unchanged.

5. PSIs throughout the day become progressively lower as the length of stay at altitude increased. The response to ACTH at sea level and high altitude appeared to be similar, but the response to a self-imposed stress was longer in duration at high altitude than at sea level.

141. Maher JT, LG Jones, LH Hartley, GH Williams and LI Rose.
Aldosterone dynamics during graded exercise at sea level and high altitude.
Journal of Applied Physiology 39:18-22, 1975.

Authors' Abstract

Hormonal responses to graded exercise of eight low altitude residents were examined at sea level (SL) and after 1 (acute) and 11 (chronic) days at 4,300 m (HA). Caloric, water, and electrolyte intakes were controlled, as were temperature and humidity. Blood was sampled at rest and during light and moderate upright bicycle exercise (20 min at 40% and 75% of maximal O_2 uptake, respectively). Mean $\dot{V}O_{2max}$ at HA was 27% lower than at SL. Resting plasma levels of aldosterone (Aldo), renin, and angiotensin II (AII) were significantly lower ($P<0.05$) on day 1 at HA compared to SL, but returned to SL values by day 11. Plasma cortisol values at rest were similar at SL and HA and were not significantly altered by light or moderate exercise. Renin, AII, and Aldo rose progressively with increasing workload in each environment. With acute HA, renin and Aldo were lower than at either SL or chronic HA. The chronic HA levels tended to approximate SL findings, implying adaptation. The data suggest that aldosterone is predominantly under the control of the renin-angiotensin system during graded exercise at sea level; and that the response of this system is altered on acute high-altitude exposure.

142. Malhotra MS, HD Brahmachari, K Sridharan, T Purshottam, K Ramachandran and U Radhakrishnan.
Electrolyte changes at 3500 m in males with and without high-altitude pulmonary edema.

Aviation, Space, and Environmental Medicine 46:409-412, 1975.

Authors' Abstract

Ten normal healthy male subjects between 20-30 years of age were initially examined at Delhi (200 m) and thereafter airlifted to an altitude of 3,500 m. Excretion of sodium, potassium and chloride in urine and their plasma level were determined at sea level (SL) and daily at high altitude (HA) for 4 d. At HA, four subjects developed high-altitude pulmonary edema (HAPE), four remained normal, and two suffered from acute mountain sickness. The results on normals and HAPE are presented. There was increased excretion of potassium at HA in both groups resulting in reduction of plasma level. The sodium and chloride excretion was also increased in normals at HA irrespective of urine volume. In HAPE cases, the sodium and chloride excretion was related to urine output. With the retention of fluid, the excretion of these ions in urine was diminished without a parallel change in plasma levels.

143. Malhotra MS, W Selvamurthy, SS Purkayastha, AK Mukherjee, L Mathew and GL Dua.
Responses of the autonomic nervous system during acclimatization to high altitude in man.
Aviation, Space, and Environmental Medicine 47:1076-1079, 1976.

Authors' Abstract

A study has been conducted on 20 sojouners, between the ages of 20-30 years, to evaluate responses of the autonomic nervous system during acclimatization to high altitude. The responses measured consisted of heart rate (HR), blood pressure (BP), oral temperature (T_{or}), mean skin temperature (T_{sk}), cold pressor response (CPR), orthostatic tolerance to tilt, and urinary catecholamines. The subjects were tested initially at Delhi (altitude 260 m) and, thereafter, on acute induction to an altitude of 3560 m periodically for 3 weeks. For comparison, the same responses were studied on 10 acclimatized lowlanders (AL) who had been staying at the same altitude for more than a year and on 10 high-altitude natives (HAN). The studies showed a rise in HR, BP, T_{or}, and urinary catecholamines, and a fall in T_{sk}, CPR, and orthostatic tolerance immediately on arrival at HA, indicating a relative hyperactivity of the sympathetic system. After a stay of 1 week, there was a gradual recovery in all the responses, though sympathetic hyperactivity was still maintained throughout the 3 weeks of stay. In AL also there was a preponderance of sympathetic activity, though of relatively lesser magnitude than that seen in sojourners. In HAN, on the other hand, there was a relative parasympathetic predomination. It has been concluded that in lowlanders it takes more than a year of stay at altitude for complete recovery of autonomic balance.

144. Mandelbaum IM, P Fondu, Ch Heyder-Bruckner, A Van Steirteghem and S Kabeya-Mudiay.
Erythrocyte enzymes and altitude.
Biomedicine 19:517-520, 1973.

Authors' Abstract

The activities of erythrocyte glucose-6-phosphate dehydrogenase (G6PD), hexokinase (HK) and pyruvate-kinase (PK) are significantly higher in healthy subjects living in villages located along the western shore of Lake Kivu (altitude I- 460 to 2000 m) than in healthy subjects living in Brussels (altitude 90 m). This phenomenon is obvious in 2 genetically well different groups (Bashi and Belgians). No difference is found for 6-phosphogluconate dehydrogenase (6PGD). The differences of activity are attributed to the effect of altitude. The mechanisms involved and the role of these modifications are discussed.

145. Maresh CH, BJ Noble, KL Robertson and JS Harvey Jr.
Aldosterone, cortisol, and electrolyte responses to hypobaric hypoxia in moderate-altitude natives.
Aviation, Space, and Environmental Medicine 56:1078-1084, 1985.

Authors' Abstract

Serum aldosterone, cortisol, and electrolyte concentration; and urinary aldosterone and electrolyte excretion responses were examined in seven low-altitude natives (LAN), (373 m or less, aged 19-25 yr) and nine moderate-altitude natives (MAN), (1,830-2,200 m, aged 19-23 yr) for 2 d at their own residence (home) altitude (P_B 740 or 585 mm Hg, respectively): and later for 2 d during

decompression at a simulated altitude of 4,270 m (P_B 447 mm Hg). The LAN group demonstrated higher ($p<0.05$) serum cortisol concentrations and respiration rates, and lower ($p<0.05$) serum aldosterone and potassium, and urinary aldosterone, sodium, and potassium concentrations at certain times during decompression compared to their home responses. Moderate-altitude native responses, on the other hand, were generally unchanged. Manifestations of acute mountain sickness at P_B 447 mmHg were also significantly greater in the LAN group. Thus, it appears that the MAN subjects were influenced less by the drop in ambient oxygen tension associated with P_B 447 mmHg.

146. Maresh CM, BJ Noble, KL Robertson and RL Seip.
Adrenocortical responses to maximal exercise in moderate-altitude natives at 447 Torr.
Journal of Applied Physiology 56:482-488, 1984.

Authors' Abstract

Serum hydrocortisone and aldosterone (Aldo) responses to maximal exercise were examined in six low-altitude natives (LAN), (373 m or less, aged 19-25 yr) and eight moderate-altitude natives (MAN), (1,830-2,200 m, aged 19-23 yr) at their residence (home) altitudes (740 and 587 Torr, respectively): and later in a hypobaric chamber at a simulated altitude of 4,270 m (447 Torr). After 2 days at their respective residence altitude and in the chamber, each subject exercised to voluntary exhaustion on the bicycle ergometer. Fluid intake was similar in both groups at all testing locations. Preexercise 24-h urinary Aldo was lower in both groups at 447 Torr, but only significantly reduced in the LAN group. In general, the changes in maximum exercise cardiorespiratory variables were twice as large in LAN as in MAN subjects going from residence altitude to 447 Torr. Both serum hydrocortisone and Aldo concentrations were increased ($P<0.01$) after exercise in both groups at residence altitude and 447 Torr. Aldo was lower ($P<0.05$) postexercise at 447 Torr than at residence altitude in both groups, but this decrease was more pronounced ($P<0.01$) in the LAN group. Thus it appears that high-altitude Aldo concentrations are more like resident altitude values in MAN than LAN subjects.

147. McDonald RK and VC Kelley.
Effects of altitude anoxia on renal function.
American Journal of Physiology 154:193-200, 1948.

Authors' Abstract

Five dogs were subjected to renal function studies at ground level and at simulated altitudes of 18,000 ft and of 24,000 ft. In all cases C_{PAH} determinations were started five minutes after reaching the desired altitude. In the case of the group 2 animals, Tm_{PAH} measurements were likewise started five minutes after attaining the desired altitude, while in the case of the group 1 animals the Tm_{PAH} measurements were started approximately 75 minutes after attaining the desired altitude. The glomerular filtration rate in these animals was either increased, decreased or unaffected depending upon the reaction of the individual animal to reduced ambient pressure. The effective renal plasma flow was increased in all dogs at an altitude of 18,000 feet and was further increased in one dog, but decreased below the ground level values in the remaining dogs at 24,000 feet. The maximum tubular excretory ability was markedly increased at 18,000 feet in 1 animal and at 24,000 feet in 2 of the 5 animals studied.

148. McFarland RA and HT Edwards.
The effects of prolonged exposures to altitudes of 8,000 to 12,000 feet during Trans-Pacific flights.
Journal of Aviation Medicine 8:156-177, 1937.

Authors' Abstract

This investigation was carried out on a routine flight of the Pan American Clipper Ship between Alameda, California and Manila, P.I., and return in order to analyze the effects of prolonged exposures to altitudes averaging 9,460 feet on seventeen airmen and eleven passengers. The total flying distance of 14,141 nautical miles involved 122 ½ hours in the air. A series of physiological, biochemical and psychological studies were made during the flights and at the various Island stations. The following conclusions may be drawn from the data obtained on these airmen and passengers:

1. These subjects, both airmen and passengers, maintained a high degree of neurocirculatory efficiency throughout the flight as judged by the individual items and composite score of the Schneider index. When the test was given in the basal state; i.e., before rising, none of the airmen tested below +7, a score frequently related to a significant degree of fatigue or unfitness in aviators. Out of a total number of tests in the basal state of 142, only two subjects tested below +10, the average being +13, close to the mean of +14.8 for college athletes (cf. Table VII). The basal state (fifty-four tests) was 11.5, only three tests falling below +7 throughout the flight. The mean score for the group at high altitude was +10.8. Out of a total number of ninety-six tests given at a mean altitude of 9,500 feet (seventeen airmen and eleven passengers), only four fell below +7.

2. There appeared to be a general tendency toward low blood pressure as the flight progressed, similar to that observed in acclimatized workmen at high altitude in the Andes. Six of the eight airmen had systolic blood pressures below 110 (mean age for group, thirty-two years). There was a consistant increase of 5 mmHg in systolic pressure on standing when taken in the basal state. This was, on the average, not true when taken in the non-basal state and at high altitude (cf. Table II). The initial response to the altitude during the flights usually showed an increase in pulse rate and an increase in systolic blood pressure, followed by a well controlled fall to normal values if the subject remained at rest.

3. As the flight progressed, there was a tendency for the pulse rate to show a greater increase after exercise and a longer time (in seconds) for the pulse to return to the normal standing rate. As might be anticipated, this was also true at high altitude while in flight.

4. There was a consistent decrease in the Schnieder scores in Manila. This was related to the increased pulse rate due to the high humidity and temperature of that region. After resting two days in Manila and sleeping in air-conditioned quarters, there was an improvement in the Schneider indices. After a rest period of one week of Honolulu, there was a slight decrease in the mean Schneider index for the eight airmen.

5. The index of the minute volume of the circulation (pulse rate _ pulse pressure) indicated that the load on the heart was consistently greater at high altitude compared with sea level (Table III); and that as the flight progressed, particularly in the tropical climate of Manila, there was a gradual yet consistent increase in this index (not to be taken as a measure of cardiac output).

6. There was a tendency toward polyuria in these airmen, as commonly observed in athletes previous to competition, particularly in those who shared the greatest responsibility in handling the ship. As the flight progressed and the airmen became acclimatized, the polyuria diminished.

7. The partial pressure of oxygen and carbon dioxide in the alveolar air and arterial blood on these airmen was similar to values considered as normal for acclimatized man at similar altitudes, suggesting that the added burden of flying the ship had no impairing effect on the respiratory mechanism (cf. Table IV). The mean alveolar pO_2 in the acclimatized airmen averaged 4.8 mm higher than in unacclimatized passengers during rapid ascents to similar altitudes.

8. There was an increase of approximately 10 per cent in the red blood cells at high altitude (cf. Tables V and VI). After five to six days at sea level, the counts returned to more normal values in nine of the eleven airmen. Even after eleven days at sea level, however, two of these airmen had counts 16 per cent and 18 per cent above the usually accepted value of 5.0 million for man at sea level, suggesting a more stable acclimatization in these individuals.

9. The normal non-protein nitrogen, blood sugar and cholesterol values suggest that there was no serious upset of the protein, carbohydrate or fat metabolism of these airmen (cf. Table V). The normal values for blood sugar suggest that there was no intense emotional excitement and increased secretion of adrenalin while in flight.

10. The alterations in the psychological tests of sensory (primarily vision) and mental functions (primarily quickness of reaction time for meaningful material, close attention, and memory), on the average, showed no significant alterations at 10,000 feet to 12,000 feet compared with sea level in these airmen and in two of the passengers (cf. Table VII).

11. In general, the conclusion may be drawn from this investigation that the 17 airmen studied during typical trans-Pacific operations became acclimatized to the high altitude and maintained a high degree of mental and physical efficiency throughout the flight. The 11 passengers of average age and fitness studied, although not manifesting the same degree of acclimatization as the airmen, showed no objective signs of fatigue or physical distress.

149. McKenzie DC, LS Goodman, C Nath, B Davidson, GO Matheson, WS Parkhouse, PW Hochachka, PS Allen, C Stanley and W Ammann.
Cardiovascular adaptations in Andean natives after 6 wk of exposure to sea level.
Journal of Applied Physiology 70:2650-2655, 1991.

Authors' Abstract

Six male Quechua Indians (34.0 ±1.1 yr, 159.5 ±2.1 cm, 60.5 ±1.6 kg), life-long residents of La Raya, Peru (4,350-m altitude with an average barometric pressure of 460 Torr), were studied using noninvasive methods to determine the structural and functional changes in the cardiovascular system in response to a 6-wk deacclimation period at sea level. Cardiac output, stroke volume, and left ventricular ejection fractions were determined using radionuclide angiographic techniques at rest and during exercise on a cycle ergometer at 40, 60, and 90% of a previously determined maximal O_2 consumption. Subjects at rest were subjected to two-dimensional and M-mode echocardiograms and a standard 12-lead electrocardiogram. Hemoglobin and hematocrit were measured on arrival at sea level by use of a Coulter Stacker S^+ analyzer. After a 6-wk deacclimation period, all variables were remeasured using the identical methodology. Hemoglobin values decreased significantly over the deacclimation period (15.7 ±1.1 to 13.5 ±1.2 g/dl; P<0.01). The results indicate that the removal of these high-altitude-adapted natives from 4,300 m to sea level for 6 wk results in only minor changes to the cardiac structure and function as measured by these noninvasive techniques.

150. Meehan RT.
Renin, aldosterone, vasopressin, cortisol and urine electrolyte responses to hypoxia during exercise.
In: Hypoxia, Exercise, and Altitude. Proceedings of the 3rd Banff International Hypoxia Symposium, edited by JR Sutton, CS Houston, and NL Jones. New York: AR Liss Inc., 1983. p.A465. (Abstract).

Author's Abstract

The effect of exercise (treadmill: 0 grade, 1 mph, 1000-1600 hrs) at simulated high altitude (4,760 m) on mean arterial pressure (MAP), endocrine responses and urinary sodium and potassium excretion ($U_{Na}\dot{V}$, $U_K\dot{V}$) during normoxia (N; room air) and hypoxia (H; F_IO_2 12.5%, PaO_2 42 ±3 mmHg) was tested in seven male volunteers. A crossover study was performed during steady state conditions of H_2O, Na and K balance. After exercise, N vs H did not differ in: body weight, hematocrit P_{osm}, U_{osm}, $U_{Na}\dot{V}$, $U_K\dot{V}$ or P vasopressin. MAP was reduced during H (86 ±2 vs 92 ±4 mmHg) despite an increased heart rate (102 ±3 vs 87 ±3), p<0.05.

	Normoxia (N)		Hypoxia (H)	
	1000hrs	1600hrs	1000hrs	1600hrs
P Cort g/dl	5.8±0.9	5.1±1.3	5.8±0.9	8.2±1.3
P Aldo ng/dl	6.5±1.3	2.8±0.5*	9.3±1.2	2.3±0.2*
PRA ng/ml/hr	3.3±0.6	2.4±0.4	4.9±1.0	2.3±0.6*

*P<0.05, 1000 vs 1600, mean ±SE

Both N and H exercise abolished normal diurnal variation in P cortisol. Exercise resulted in decreases in P aldosterone and P renin activity which were greater during H than N. Conclusion: six hours of continuous low level exercise depresses the renin-angiotensin-aldosterone system. Moderate hypoxia enhances this depression and lowers MAP.

151. Meehan RT.
Renin, aldosterone, and vasopressin responses to hypoxia during 6 hours of mild exercise.
Aviation, Space, and Environmental Medicine 57:960-965, 1986.

Author's Abstract

The effect of hypoxia (H) on plasma renin (PRA), aldosterone (PA), and arginine

vasopressin levels (AVP) was evaluated during 6 h of mild exercise (treadmill: 0 grade, 1 mph). A crossover study was performed on seven male volunteers during steady state conditions of H_2O, Na^+ and K^+ balance while breathing 12.5% O_2 (PaO_2 42 ±3 mmHg) and room air (N, 21% O_2). After exercise there were no significant differences in body weight, hematocrit, calculated plasma volumes, serum or urine osmolaltiy, urine Na^+ or K^+ excretion or AVP. Mean arterial pressure (MAP) while exercising was reduced during hypoxia (86 ±2 vs. 92 ±4 mmHg, $p<0.05$). Normal diurnal variation in serum cortisol was lost during exercise (N and H). Plasma renin and aldosterone levels fell with exercise in both groups: PRA N 3.3 to 2.4 vs. H 4.9 to 2.3 $ng \cdot ml^{-1} \cdot h^{-1}$; PA N 6.5 to 2.8 vs. H 9.3 to 2.3 $ng \cdot dl^{-1}$ ($p<0.05$). Hypoxia per se did not exert influence beyond mild exercise regarding serum osmolality, urine osmolality or Na^+ or K^+ excretion. Sustained hypoxia during 6 h of mild exercise despite a lower MAP failed to elevate PRA, aldosterone, or AVP levels when normal hydration is maintained.

152. Merino CF.

Studies on blood formation and destruction in the polycythemia of high altitude.

The Journal of Hematology V:1-31, 1950.

Author's Abstract

Studies of blood formation and destruction in the polycythemia of high altitude have been carried out. Three different groups of subjects were studied:

1. Healthy adult male subjects from sea level who, after being studied at this level, were taken to an altitude of 4,540 meters (Morococha) where they developed a marked polycythemic process. When these subjects returned to sea level, the mechanisms of recuperation of the hematologic equilibrium were studied.

2. Normal adult subjects, natives of high altitude, chronically polycythemic due to their permanent residence in Morococha, who were first studied in their native town and then brought to sea level where they were observed during five weeks.

3. Subjects, residents of high altitude (Morococha), who had lost their adaptation to it; i.e., who had developed chronic altitude sickness of Soroche (Monge's malady).

The observations carried out permit the following conclusions:

1. The polycythemic process of subjects with anoxia caused by a low pressure environment is due to a greater blood formation by the hematopoietic organs. This becomes manifest after forty-eight hours. The very discreet polycythemia frequently found during the first hours is probably the result of hemoconcentration and release of stored blood.

2. This polycythemic process is not accompanied by quantitative alterations of the leukocytes nor of the platelets; thus, differing from polycythemia vera, in which there is as a rule an increase in all the hematologic elements.

3. The increased blood volume of residents at high altitude is due exclusively to the increased red cell mass, the plasma volume being more likely to be found diminished.

4. In normal subjects who are temporarily or permanently exposed to an atmosphere of low barometric pressure, the excretion of fecal urobilinogen does not exceed the limits considered normal at sea level, but increases with relation to the larger circulatory hemoglobin mass, a normal hemolytic index being maintained.

5. The hyperbilirubinemia very frequently found in the natives and in those resident for a long time at high altitudes appears to be related to a lesser excretion of this pigment by the liver, probably on the basis of the anoxic state. The greater production of bilirubin in subjects at high altitude is not sufficient to explain, in and of itself, the pigmentary elevation in the blood.

6. The mechanism of the disappearance of the polycythemia when the subjects from a high altitude are brought to sea level, appears to be as follows: (a) temporary diminution or inhibition of erythropoiesis, and (b) a greater blood destruction. The latter takes place only during the first days of stay at sea level, being chiefly responsible for the early rapid decrease of the degree of polycythemia, while the former acts in a more prolonged form and is principally responsible for the erythropoietic "normalization."

7. In two cases of chronic altitude sickness, or chronic Soroche (Monge's disease), the output of fecal urobilinogen exceeded proportionally the increase of the

circulatory hemoglobin mass. The hemolytic index was found abnormally high.

8. The above findings indicate that the polycythemia of the normal individual residing at high altitudes is characterized by a proportional and direct accentuation in the processes of blood formation and destruction. On the other hand, in those subjects also residing at high altitudes, who exhibit an abnormally high polycythemia (chronic Soroche), the accentuation in the processes of blood destruction is proportionally greater than that corresponding to the greater erythropoiesis. This characteristic constitutes a possible diagnostic criterion and can perhaps explain in part the etiologic mechanism of this alteration.

153. Merino CF and C Reynafarje.
Bone marrow studies in the polycythemia of high altitudes.
Journal of Laboratory and Clinical Medicine 34:637-647, 1949.

Authors' Abstract

The bone marrow of sixteen, healthy, Indian natives of adult age, permanent residents in Cerro de Pasco at an altitude of 4,390 meters (14,400 feet), was studied. Samples were obtained by means of sternal aspiration, and supravital and Wright stained preparations were used for the qualitative as well as quantitative microscopic examinations. All men showed a definite polycythemia in the peripheral blood.

The results obtained were compared with previous observations made in healthy people living at sea level and in patients with polycythemia vera.

1. The bone marrow of healthy, adult natives, living permanently at an altitude of 4,390 meters (14,400 feet), was interpreted as showing hyperplasia (hypercellularity) in 81.2 per cent of the subjects examined.

2. This hyperplasia was characterized by a marked increase of the cells of the erythroid series over the myeloid cells. Normoblasts were the most predominant cellular elements (normoblastic hyperplasia), and a reversed M/E ratio was a constant finding. The degree of hyperplasia was not always proportional to the level of polycythemia found in the peripheral blood.

3. Myeloid cells and megakaryocytes were not increased and the maturation process was normal in both the erythroid and myeloid series.

4. The foregoing findings seem to confirm further the opinion, previously expressed and derived from studies on peripheral blood, that anoxia acts as a specific stimulus for an increased activity in the formation of the erythroid cells leaving the myeloid cells unaffected.

5. A comparative study of our findings and those obtained in similar investigations made by several observers in cases of polycythemia vera seems to indicate that, in general, the bone marrow cytology and the degree and kind of hemopoietic hyperactivity are not similar in the polycythemia of high altitudes and in polycythemia vera. This fact does not conform with the theory that anoxia is the underlying etiologic factor in the latter disease.

154. Miles DS, DR Bransford and SM Horvath.
Hypoxia effects on plasma volume shifts at rest, work, and recovery in supine posture.
Journal of Applied Physiology 51:148-153, 1981.

Authors' Abstract

The purpose of this study was to determine the effects of acute exposure to hypoxia (<1.5 h; gas mixture 12.6% O_2-87.4% N_2) on plasma volume (PV) shifts during rest and exercise. Nine unacclimatized males performed identical protocols in the supine posture in both normoxic (N) and hypoxic (H) conditions. The protocol was rest 60 min, submaximal exercise (PWC_{140}, work rate eliciting a heart rate of 140 beats/min) for 30 min, immediately followed by maximal exercise, and 10 min of passive recovery. There were slight but significant losses of 2.7 and 1.4% PV at rest in H and N conditions, respectively. At the same relative intensity of submaximal exercise (work loads reduced by 22% in H conditions), PV losses were nearly identical (N = 11.2%, H = 11.8%). There was a further PV efflux subsequent to maximal exercise (N = 7.9%, H = 5.2%). The maximum PV efflux, from the beginning of rest to the end of maximal exercise, was 20% for both conditions. Total plasma protein (PP) content was unchanged during rest or exercise

for either N or H conditions. After 10 min of recovery, restitution of PV was 10% below preexercise values for both N and H conditions. We conclude that acute hypoxic exposure does not influence the loss of PV or PP during submaximal or maximal exercise.

155. Milledge JS.
Salt and water control at altitude.
International Journal of Sports Medicine 13:S61-S63, 1992.

Author's Abstract

The physiological effect of altitude hypoxia, in the absence of exercise, is a sodium and water diuresis with decrease in plasma and extra-cellular volumes. Plasma aldosterone concentrations (PAC) are reduced, but plasma atrial natriuretic peptide (ANP) levels are modestly increased. Day-long exercise at low altitude has almost opposite effects on fluid balance. There is an anti-diuresis, sodium retention, expansion of the plasma and extra-cellular compartments, elevation of PAC and ANP. Subjects who develop acute mountain sickness (AMS) show a pathological response to hypoxia even before the development of symptoms. There is an anti-diuresis, sodium retention, increased plasma and extra-cellular volumes and increased PAC compared with subjects resistant to AMS. Plasma ANP tends to be elevated compared with sea level values, but the relation of ANP levels to AMS is variable. In general therefore, the pathological response to altitude hypoxia parallels that of exercise at low altitude and is opposite to the physiological response. Both exercise and the pathological response predispose the subject to edema and are probably important in the genesis of AMS.

156. Milledge JS, JM Beeley, S McArthur and AH Morice.
Atrial natriuretic peptide, altitude and acute mountain sickness.
Clinical Science 77:509-514, 1989.

Authors' Abstract

1. To investigate the mechanisms of acute mountain sickness, 22 subjects travelled to 3100 m by road and the following day walked to 4300 m on Mount Kenya. Control measurements were made over 2 days at 1300 m before ascent and for 2 days after arrival at 4300 m. These included body weight, 24 h urine volume, 24 h sodium and potassium excretion, blood haemoglobin, packed cell volume, and symptom score for acute mountain sickness. In 15 subjects blood samples were taken for assay of plasma aldosterone and atrial natriuretic peptide.

2. Altitude and the exercise in ascent resulted in a marked decrease in 24 h urine volume and sodium excretion. Aldosterone levels were elevated on the first day and atrial natriuretic peptide levels were higher on both altitude days compared with control.

3. Acute mountain sickness symptom scores showed a significant negative correlation with 24 h urinary sodium excretion on the first altitude day. Aldosterone levels tended to be lowest in subjects with low symptom scores and higher sodium excretion. No correlation was found between changes in haemoglobin concentration, packed cell volume, 24 h urine volume or body weight and acute mountain sickness symptom score.

4. Atrial natriuretic peptide levels at low altitude showed a significant inverse correlation with acute mountain sickness symptom scores on ascent.

157. Milledge JS, EI Bryson, DM Catley, R Hesp, N Luff, BD Minty, MWJ Older, NN Payne, MP Ward and WR Withey.
Sodium balance, fluid homeostasis and the renin-aldosterone system during the prolonged exercise of hill walking.
Clinical Science 62:595-604, 1982.

Authors' Abstract

1. The effect of 5 consecutive days of hill walking on electrolyte balance, fluid homeostasis, plasma renin activity and plasma aldosterone concentration was studied in five male subjects.

2. The 5-day exercise period was preceded by a 4-day control period and followed by a 4-day recovery period. Throughout the 13-day study subjects ate a fixed diet.

3. After 5 days of exercise subjects had retained a mean of 264 mmol (SD 85) of sodium. Plasma sodium concentration remained constant at 142.0 mmol/l (SD 5.4). This indicates an expansion of the extracellular space by 1.84 litres.

4. By the end of the exercise period there was a positive water balance of about 0.9 litre.

Thus there was a net movement of 0.94 litre of fluid from the intracellular to the extracellular space.

5. Packed cell volume decreased from a mean of 43.5% to 37.9% after 5 days of exercise, indicating that about 0.9 liter of the extracellular fluid entered the vascular compartment. The remaining fluid may be responsible for the significant increase in lower leg volume.

6. During the exercise period plasma aldosterone concentration and plasma renin activity rose, and there was a highly significant correlation between these values and the sodium retention. There was also a significant correlation between sodium retention and the increase in leg volume, which suggests that oedema may be the result of prolonged exercise of this type.

158. Milledge JS and DM Catley.

Renin, aldosterone, and converting enzyme during exercise and acute hypoxia in humans.

Journal of Applied Physiology 52:320-323, 1982.

Authors' Abstract

The possibility that hypoxia might inhibit the secretion of angiotensin-converting enzyme (ACE) would explain the low concentrations of aldosterone reported in humans at high altitude. To observe the effect of such a reduction in ACE concentration on the plasma aldosterone concentration (PAC); four subjects performed mild exercise throughout a 2-h study so as to elevate their plasma renin activity (PRA). After the first 60 min breathing air, they were switched to breathing 12.8% O_2 (4,000 m altitude equivalent). Venous samples were taken at intervals for hormone analysis. Results showed the expected rise of PRA and PAC both tending toward a plateau after about 45 min. There was no significant change in ACE activity (F = 0.065). Hypoxia produced a further 50% rise in PRA but a fall in PAC and 30% reduction in ACE activity. Angiotensin I concentrations closely followed PRA throughout (r = 0.984). These results indicate, that during exercise, acute hypoxia changes the usual close relationship between PAC and PRA by reducing ACE activity.

159. Milledge JS and DM Catley.

Angiotensin converting enzyme response to hypoxia in man: its role in altitude acclimatization.

Clinical Science 67:453-456, 1984.

Authors' Abstract

1. The response of serum angiotensin converting enzyme (ACE) activity to three grades of hypoxia was studied in two groups of human subjects. Hypoxic gas mixtures having oxygen concentrations of 14, 12.6 and 10.4% were breathed successively for a period of 10 min at each concentration. Venous blood was sampled at the end of each of the three periods and arterial oxygen saturation was recorded throughout the experiment.

2. The subjects were selected as being 'good' or 'poor' acclimatizers according to their history of acute mountain sickness. There were five subjects in each group.

3. Hypoxia resulted in a reduction in ACE activity in both groups, the reduction being linear with respect to arterial oxygen saturation.

4. The reduction in ACE activity was greater in the good acclimatizer group as shown by a significantly greater slope of the response line of ACE activity to arterial oxygen saturation.

5. The significance of this finding in relation to the mechanism underlying acute mountain sickness is discussed.

160. Milledge JS and DM Catley.

Angiotensin converting enzyme activity and hypoxia.

Clinical Science 72:149, 1987.

Authors' Abstract

Subsequent to the publication of our paper on serum angiotensin converting enzyme activity (ACE) and hypoxia, we have further investigated this effect in man in one study at altitude and five laboratory studies at sea level.

In the study at altitude (4100 m), in six subjects a total of 12 sea level and 56 altitude serum samples were taken. In the five laboratory studies, nine subjects (some studied on a number of occasions) breathed low oxygen gas mixtures (14-10% O_2 for periods up to 30 min): 26 control and 36 hypoxic serum samples were collected. Samples were analysed in our own laboratory by the Friedland & Silverstein fluorimetric method and also by Dr. R. Bird at the Royal Northern Hospital using the same method. In the last

four laboratory studies (32 serum samples), the same samples were also analysed by Mr C. Dickens of the Clinical Chemistry Department here, using a centrifugal analyser method.

The results of all these studies showed that hypoxia, induced either by going to altitude or by breathing hypoxic gas mixtures at sea level, had no effect on serum ACE activity. In addition, Dr J.W. Ryan of the Department of Medicine, University of Miami, re-analysed some archived serum samples from an earlier unpublished study using his radioactive substrate method and also found no difference between control and hypoxic samples.

We cannot account for our earlier findings demonstrating an effect of hypoxia on serum ACE activity. We believe that the true situation is that hypoxia, acute or chronic, has no effect and we wish to retract the findings that we published previously.

Recently other investigators have shown that hypoxia does not effect ACE activity. These support the previous work of Pitt & Lister and Catravas & Gillis, and the most recent paper on the subject found only some 20% reduction in transpulmonary conversion of ANG I to ANG II in hypoxia. One paper claiming an effect in endothelial cell culture has been withdrawn.

Our starting observation, that hypoxia reduces the aldosterone response to a rise in plasma renin activity, has been confirmed. This would seem not to be due to any reduction in ACE activity as was first suggested, and the mechanism remains unexplained.

161. Milledge JS, DM Catley, FD Blume and JB West.
Renin, angiotensin-converting enzyme, and aldosterone in humans on Mount Everest.
Journal of Applied Physiology 55:1109-1112, 1983.

Authors' Abstract

Plasma renin activity (PRA), serum angiotensin-converting enzyme (ACE) activity, and plasma aldosterone concentration (PAC) were measured in 15 subjects at sea level and at high altitude. Previous work has shown that, on first ascent to altitude, PAC and ACE are reduced, whereas PRA may be raised or reduced. After 2-4 wk at 6,300 m all hormones had returned to within ±10% of sea-level values. In seven subjects PRA and PAC were measured when exercise stopped. PRA and PAC were both elevated, PRA more than PAC; i.e., the PAC response to PRA was markedly blunted. Since ACE activity was normal, it is suggested that there may be down regulation, i.e., reduction in density of angiotensin II receptors on the adrenal cortex and/or induction of enzymes which degrade angiotensin II. This mechanism apparently protects the subjects from very high levels of PAC and sodium retention when hypoxia and exercise raise PRA to very high levels.

162. Milledge JS, DM Catley, MP Ward, ES Williams and CRA Clarke.
Renin-aldosterone and angiotensin-converting enzyme during prolonged altitude exposure.
Journal of Applied Physiology 55:699-702, 1983.

Authors' Abstract

The effect of 7 week altitude exposure on plasma renin activity (PRA), plasma aldosterone concentration (PAC), and angiotensin-converting enzyme (ACE) activity was studied in 10 male subjects at 4,500 m. There was an initial increase in PRA and a reduction in PAC and ACE. The reduction in ACE was significantly greater in the four subjects who had frequently been exposed to extreme altitudes than in the other six subjects. These changes had returned to control values between 12 and 20 days. Exercise caused a marked elevation of PRA and PAC, but the PAC response to PRA was blunted compared with that at sea level. The ratio PAC/PRA at rest was reduced initially but returned to control values with a similar time course to that of ACE activity. The results are compatible with the hypothesis that ACE activity governs the adrenal response to PRA.

163. Milledge JS, DM Catley, ES Williams, MP Ward, CRA Clarke, JB West and FD Blume.
The effect of chronic hypoxia on the renin-aldosterone system in man.
In: Hypoxia, Exercise, and Altitude. Proceedings of the 3rd Banff International Hypoxia Symposium, edited by JR Sutton, CS Houston, and NL Jones. New York:

AR Liss Inc., 1983. p.A465-A466. (Abstract).

Authors' Abstract

Expeditions to Mt. Kongur (7,719m) in China and to Mt. Everest afforded opportunities to study the effect of chronic hypoxia on the renin-aldosterone system in man. Plasma and serum samples both at rest and on stopping exercise were collected for the measurement of plasma renin activity (PRA), plasma aldosterone concentration (PAC) and angiotensin converting enzyme (ACE) activity. At 4,500m in resting subjects during the initial 10 days at altitude, PRA was raised and PAC and ACE activity were reduced. By 20 days all these hormones had returned to control values. Thereafter, all three tended to rise with ACE being 23% above control after 7 weeks. On Everest after 2-4 weeks at 6,300m, the levels of all three hormones had returned to sea level values. Samples taken on stopping exercise showed elevated PRA and PAC values, but the PAC response to a rise in PRA was blunted. This could be attributed to reduced ACE activity in the first 12 days at altitude on Kongur, but on Everest this blunted response was seen with ACE activity slightly above control values. It is suggested that the rapid reduction of ACE activity with acute hypoxia provides emergency regulation of the system. Longer term regulation may be provided by down regulation of Angiotensin II receptors or enzyme induction.

164. Milledge JS, DM Catley, ES Williams, WR Withey and BD Minty.

Effect of prolonged exercise at altitude on the renin-aldosterone system. *Journal of Applied Physiology* 55:413-418, 1983.

Authors' Abstract

The combined effect of exercise and altitude on the renin-aldosterone system was studied in six male subjects on a fixed diet. After 4 control days at rest and at low altitude, subjects ascended to 3,100 m and took about 7 h exercise daily for 5 days. There followed a 4-day recovery period at low altitude. Daily blood samples were taken for estimation of plasma renin activity (PRA), plasma aldosterone concentration (PAC), and angiotensin converting-enzyme (ACE) activity. Results showed a maximal rise in PRA and PAC with exercise at altitude maximal on the first 2 days. ACE activity fell by 23% at altitude. Compared with similar exercise at sea level, the rise in PAC was comparable but the rise in PRA was four times greater, indicating a marked decrease in PAC response to PRA. It is suggested that this loss of sensitivity of PAC to PRA is mediated by the measured reduction in ACE activity.

165. Milledge JS and PM Cotes.

Serum erythropoietin in humans at high altitude and its relation to plasma renin. *Journal of Applied Physiology* 59:360-364, 1985.

Authors' Abstract

Serum immunoreactive erythropoietin (siEp) was estimated in samples collected from members of two scientific and mountaineering expeditions; to Mount Kongur in Western China and to Mount Everest in Nepal. SiEp was increased above sea-level control values 1 and 2 days after arrival at 3,500 m and remained high on ascent to 4,500 m. Thereafter, while subjects remained at or above 4,500 m, siEp declined; and by 22 days after the ascent to 4,500 m was at control values, but increased on ascent to higher altitude. Thus siEp was at normal level during the maintenance of secondary polycythemia from high-altitude exposure. On descent, with removal of altitude hypoxia, siEp decreased; but despite secondary polycythemia levels, remained measurable and in the range found in subjects normally resident at sea level. On Mount Everest, siEp was significantly ($P<0.01$) elevated above preexpedition sea-level controls after 2-4 wk at or above 6,300 m. There was no correlation between estimates of siEp and plasma renin activity in samples collected before and during both expeditions.

166. Milles JJ, PH Baylis, AR Bradwell and Birmingham Medical Research Expeditionary Society.

Vasopressin and H_2O excretion at high altitude. *In: Hypoxia, Exercise, and Altitude. Proceedings of the 3rd Banff International Hypoxia Symposium,* edited by JR Sutton, CS Houston, and NL Jones. New York: AR Liss Inc., 1983. p. A466-A467. (Abstract).

Authors' Abstract

Plasma vasopressin (pVP) was measured daily in 17 males during a high-altitude trek to 5000m. At the highest altitudes pVP was low (1.7 ±1.1 pg/ml) and not elevated in the three subjects most affected by acute mountain sickness (AMS).

In the second study 20 males were water loaded at different altitudes up to 5000 m. Half took acetazolamide sustained release (500 mg/day) and half a placebo. There was a significant reduction in the percentage of the water load excreted at higher altitudes: 90.8 ±5.2% (mean ±SEM) at 150 m vs 59.3 ±7.2% (placebo group) $p<0.01$, and 65.4 ±3.5% (acetazolamide group); but this difference did not significantly correlate with the severity of AMS ($p>0.05$). Low urine osmolarities were achieved during water loading at different altitudes and were not significantly different ($p>0.05$).

These results suggest that excess vasopressin does not contribute to water retention at high altitude or to the development of AMS.

167. Moncloa F, L Beteta, I Velazco and C Goñez.
ACTH stimulation and dexamethasone inhibition in newcomers to high altitude.
*Proceedings of the Society for Experimental Biology and Medicine*122:1029-1031, 1966.

Authors' Abstract

Previous work from this laboratory has shown that sea level residents exposed to high altitude increase their cortisol secretion rate; however, the response of the adrenal cortex was not maximal (1). This may represent: 1) a not intense enough stimulation, or 2) adrenal inability of a greater response. The present investigation was undertaken in an effort to answer this question, and also to study whether dexamethasone was able to prevent the transitory hyperactivity of the adrenal when sea level residents are exposed to high altitude.

168. Moncloa F, A Carcelen and L Beteta.
Physical exercise, acid-base balance, and adrenal function in newcomers to high altitude.
Journal of Applied Physiology 28:151-155, 1970.

Authors' Abstract

Newcomers to high altitude show a significant and inverse correlation between Pa_{O2} and either plasma cortisol, urinary 17-OHCS, or urinary 17-KGS. No correlation was demonstrable between Pa_{CO2} or pH and indexes of adrenal function. These results are interpreted as indicative that the adrenal hyperactivity at high altitude is not dependent on alkalosis. During exercise acidosis is more severe than at sea level; and it is associated with a significant decrease in plasma cortisol not observed at sea level. No variation in glucose concentration occurred at high altitude in contrast to a decrease at sea level.

169. Moncloa F, J Donayre, LA Sobrevilla and R Guerra-García.
Endocrine studies at high altitude II. Adrenal cortical function in sea level natives exposed to high altitudes (4300 meters) for two weeks.
Journal of Clinical Endocrinology 25:1640-1642, 1965.

Authors' Abstract

Ten young adult males were exposed to 4300 meters of altitude for 2 weeks. Urinary 17-ketogenic steroids (17-KGS), 17-hydroxycorticosteroids (17-OHCS), and the cortisol secretion rate were transitorily increased. Urinary 17-ketosteroids (17-KS) were not significantly modified. The changes observed in 17-OHCS with exposure to high altitude are similar to those found with an 8-hr intravenous infusion of 1 U of ACTH. Possible interpretations of the observed dissociation between 17-KS and the other variables studied are discussed.

170. Moncloa F, I Velasco and L Beteta.
Plasma cortisol concentration and disappearance rate of 4-^{14}C-cortisol in newcomers to high altitude.
Journal of Clinical Endocrinology 28:379-382, 1968.

Authors' Abstract

Cortisol plasma concentration, volume of distribution, metabolic clearance rate and the fractional turnover rate constants have been studied in young male sea level natives before and during exposure to 4300 m of altitude. The second day of stay at high altitude the mean plasma cortisol concentration increased from 9.9 ±0.6 to 15.5 ±3.1 g/100 ml ($p<0.05$). The estimated metabolic clearance rate was not significantly altered: 239.5 ±22.7 l/24 hr for sea level control vs. 259.7 ±15.8 l/24 hr during exposure to high altitude. The cortisol is distributed between 2 compartments; the second compartment decreased during exposure to high altitude from 11.7 ±1.5 to 7.1 ±1.0 L ($p<0.02$). This decrease may be partially explained as a consequence of contraction in the extracellular space.

171. Monge CC, R Lozano and A Carcelén.
Renal excretion of bicarbonate in high altitude natives and in natives with chronic mountain sickness.
Journal of Clinical Investigation 43:2303-2309, 1964.

Authors' Abstract

When compared with sea level controls, natives from high altitudes (4,300 m above sea level) have lower arterial Pco_2 and the same renal maximal reabsorption (Tm) of bicarbonate. Natives with chronic mountain sickness have a higher arterial Pco_2 than their own native control group and a higher bicarbonate Tm. The results are interpreted as indicating that the normal high altitude native is in a new state of acid-base equilibrium. The possible roles of high arterial Pco_2, hypokalemia, and anoxia in the elevation of bicarbonate Tm of patients with chronic mountain sickness are discussed.

172. Monge CC, R Lozano, C Marchena, J Whittembury and C Torres.
Kidney function in the high-altitude native.
Federation Proceedings 28:1199-1203, 1969.

Annotation

Purpose

To investigate the structural and physiological factors that influence the circulatory and renal function of humans born and living at high altitude vs. humans born and living at sea level.

Methods

Metabolic alkalosis was induced in 17 volunteers:

6 normal at sea level
6 normal high-altitude natives (4,300 m)
5 high altitude natives (4,300 m) with chronic mountain sickness

Blood acid-base status and bicarbonate tubular maximum were assessed.

Metabolic acidosis was induced by intravenous infusion of ammonium chloride in 6 normal sea-level residents and in 6 normal high altitude natives (4,300 m). Ten parameters related to acid-base equilibrium were studied.

Small amounts of synthetic angiotensin was infused intravenously to 14 volunteers which included: 6 normal sea-level residents studied at Lima (sea-level), and 8 normal high-altitude natives studied in Morococha (4,500 m).

Results

When metabolic alkalosis was induced: 1) normal high-altitude natives showed a low pCO_2 and also a slightly alkaline pH. 2) chronic mountain sickness, high altitude natives and sea-level volunteers exhibit similar pCO_2 status, indicating hypoventilation.

After bicarbonate loading the three groups developed a marked increase in pH. Patients with chronic mountain sickness exhibited high comparative values of bicarbonate reabsorption to compensate for high arterial pCO_2.

When metabolic acidosis was induced: 1) normal sea-level residents and normal high altitude natives (4,300 m) exhibited similar acid-base equilibrium responses. 2) both groups also had a similar decrease in urine ammonium excretion.

When angiotensin was infused intravenously: 1) reduction of filtration rate and renal plasma flow was observed in both groups, but it was of much lesser magnitude in high-altitude natives; 2) as with reabsorption of bicarbonate and the secretion of hydrogen ions, the tubular capacity of the high altitude kidney to reabsorb sodium in the presence of angiotensin was not impaired.

Conclusions

These findings indicated the great capacity of the kidney to maintain adequate tubular function in the presence of extreme reduction of plasma flow, greatly increased blood viscosity, marked hypoxemia, and possible anatomical changes to accommodate a larger amount of blood.

The correlative studies between arterial pCO_2 and renal bicarbonate tubular maximum (Tm) in steady-state conditions of hyperventilation and relative hypoventilation indicate the need to study the clinical respiratory condition at sea level, which so far has not been investigated from this point of view. Finally, the response of angiotensin in the high altitude native could be used in an attempt to clarify the paradoxical response (natriuresis) which is produced in hypertensives and cirrhotics when angiotensin is infused.

The reduced filtration rate and plasma flow, elevated filtration fraction, and lack of reduction of total blood flow favor the view that the natriuresis can be explained more by renal ischemia than by an elevated filtration fraction.

173. Myhre LG, DB Dill, FG Hall and DK Brown.

Blood volume changes during three-week residence at high altitude.
Clinical Chemistry 16:7-14, 1970.

Authors' Abstract

Circulating red blood cell volumes were determined by the carbon monoxide method and plasma volumes were calculated in four men 20, 29, 71, and 75 years old, and two women 29 years of age before, during, and after exposure to an altitude of 3800 m. In the four youngest subjects there were early increases in hemoglobin concentration during the first days at the stated altitude attributed to decreases in plasma volume. At the same time, hemoglobin concentration decreased and plasma volume increased in the oldest subject. Red cell volumes were slow to change, and it was concluded that 3 weeks or more of exposure to this altitude are required to affect significantly the red cell volume in man.

174. Okazaki S, Y Tamura, T Hatano and N Matsui.

Hormonal disturbances of fluid-electrolyte metabolism under altitude exposure in man.
Aviation, Space, and Environmental Medicine 55:200-205, 1984.

Authors' Abstract

Early alterations in fluid, electrolytes, and their regulating hormones were investigated in men exposed to 6,000 m simulated altitude (2 h-ascent, 2 h-sojourn, 2 h-return). Hematocrit and serum protein rose with elevated serum osmolality and reduced urine flow upon arrival at 6,000 m, suggesting decreased plasma volume probably due to a hypotonic fluid shift to the intracellular space. Serum K^+ declined reflecting respiratory alkalosis. The exposure raised plasma antidiuretic hormone (ADH), plasma renin activity (PRA), serum cortisol and aldosterone. Increases both in ADH and aldosterone showed close correlations with that in cortisol, suggesting that ADH may be elevated by hypoxic stress in addition to elevated serum osmolality and decreased plasma volume, and that increased secretion of adrenocorticotropin may be the main cause of increased aldosterone, though PRA involvement cannot be excluded. These rises in ADH and aldosterone may act to retain body water, and the latter may exaggerate alkalosis; thus, these hormonal changes may be related to acute mountain sickness.

175. Pace N, RL Griswald and BW Grunbaum.

Increase in urinary norepinephrine excretion during 14 days sojourn at 3,800 meters elevation.
Federation Proceedings 23:521, 1964. (Abstract).

Authors' Abstract

Urinary excretion rates of epinephrine (EP) and norepinephrine (NE) were measured in 6 men. After 3 days in Berkeley (100 meters), the subjects were taken to the Barcroft

Laboratory of the White Mountain Research Station (3,800 meters) where measurements were made for 14 days. Little change occurred in EP excretion rate, other than expected diurnal variation. In contrast, NE excretion rate increased steadily, starting the 2nd day at Barcroft, to twice that at sea level by the end of the 14 day sojourn (58.9 g/24 hr compared with a mean sea level value of 30.8 g/24 hr). Although the bulk of the increase occurred during the day, an increase was also noted in the overnight period. Mean resting heart rate rose from 69/min at sea level to 92/min by the 2nd day at altitude, then gradually fell to 87/min by the 14th day. Neither NE excretion rate nor heart rate had returned to original sea level values by the 4th day after the altitude sojourn. These data are interpreted as evidence for a substantial and continuing response of the sympathetic nervous system during at least the first 14 days at high altitude. They also indicate some measure of functional adaptation to increased NE production.

176. Pauli HG, B Truniger, JK Larsen and RO Mulhausen.
Renal function during prolonged exposure to hypoxia and carbon monoxide
I. Glomerular filtration and plasma flow.
Scandinavian Journal of Clinical and Laboratory Investigation Suppl. 103:55-60, 1968.

Authors' Abstract

Prolonged exposure of normal subjects to hypoxia and to carbon monoxide seem to affect renal function differently. During a 10- day sojourn at medium altitude (3454 meters above sea level), a diminution of effective renal plasma flow of borderline significance was observed while glomerular filtration rate remained close to control levels. Changes in glomerular filtration rate and effective renal plasma flow, leading to the well known pattern of fully acclimatized subjects or high altitude dwellers, seem to follow a slow time course. An acute increase of glomerular filtration rate and, less consistently, of effective renal plasma flow was observed within the first 36 hours of prolonged exposure to carbon monoxide, while changes during the remainder of an 8-day exposure period were equivocal. Possible explanations of this phenomenon are changes in intrarenal vasomotor tone and/or in glomerular membrane permeability.

177. Pauli HG, B Truniger, JK Larsen and RO Mulhausen.
Renal function during prolonged exposure to hypoxia and carbon monoxide
II. Electrolyte handling.
Scandinavian Journal of Clinical and Laboratory Investigation 22:61-67, 1968.

Authors' Abstract

Studies of renal electrolyte handling under conditions of prolonged hypoxia indicate an increase in sodium and chloride elimination due to elevated tubular rejection of these electrolytes, mainly during the first 24 hours after arrival at altitude; while potassium elimination appears to be affected in a converse manner. Renal tubular electrolyte handling values in the initial phase of prolonged exposure to CO were consistent with a regulatory response to primary elevation of GFR.

178. Picón-Reátegui E.
Basal metabolic rate and body composition at high altitudes.
Journal of Applied Physiology 16:431-434, 1961.

Author's Abstract

Basal metabolic rate (BMR) and body composition were determined in 17 healthy adult males living at an altitude of 14,900 ft above sea level. Using body surface area as a standard of reference and following the criterion of Boothby et al. (Am. J. Physiol. 116:468, 1936), the BMR of the high-altitude resident fell within the limits considered normal for healthy adults at sea level. A comparison with the data obtained by investigators in the United States and in India shows that, when either fat-free body mass (FFM), cell mass (C),or cell solids (S) are the standard of reference, the BMR is higher in the high-altitude resident. The higher O_2 consumption per kilogram of FFM, C, or S in the high-altitude resident seems to be one of the many mechanisms developed by the body in its process of adaptation to the low O_2 tension.

179. Picón-Reátegui E, R Lozano and J Valdivieso.
Body composition at sea level and high altitudes.
Journal of Applied Physiology 16:589-592, 1961.

Authors' Abstract

Simultaneous determinations of total body water and extracellular fluid, using the antipyrine and sucrose infusion methods, have been carried out in 28 adult male residents at sea level and in 28 residents at an altitude of 14,900 ft. Body composition was calculated from these data. The various body spaces expressed in percentage of body weight, were similar in the two groups, with the exception of the extracellular fluid which was greater in those in the high altitude group ($P<0.01$). Neither racial characteristics nor altitude appear to be factors generally affecting body composition. In individuals having adequate caloric intake, body composition seems to be influenced principally by physical activity. In fact, physical inactivity appeared to produce a loss of active tissue and its replacement by fat.

180. Pines A, JDH Slater and TP Jowett.
The kidney and aldosterone in acclimatization at altitude.
British Journal of Chest Disease 71:203-207, 1977.

Authors' Abstract

Five climbers were studied during an ascent of a 7,500 m mountain in the Hindu Kush. Representative samples from 24-hour urines were preserved from five subjects at 5,400 m and 6,600 m, and from two at 7,000 m. Sodium and cortisol excretion was normal, but that of potassium and especially aldosterone was low, especially in two climbers who had episodes of peripheral oedema. Hypoaldosteronism is a feature of high altitude acclimatization, but its cause and significance have still to be elucidated.

181. Porchet M, H Contat, B Waeber, J Nussberger and HR Brunner.
Response of plasma arginine vasopressin levels to rapid changes in altitude.
Clinical Physiology 4:435-438, 1984.

Authors' Abstract

Plasma arginine vasopressin levels were studied in 15 normal working men exposed at 4-day intervals to a rapid increase or decrease in altitude of 2000 m.

Plasma arginine vasopressin levels were significantly lower ($P<0.001$) at the higher altitude though plasma osmolality did not change.

It is concluded that the important diuresis known to occur physiologically in response to high altitude may be related to a decrease in antidiuretic hormone release.

182. Pugh LGCE.
Physiological and medical aspects of the Himalayan Scientific and Mountaineering Expedition, 1960-61.
British Medical Journal, September 8, 1962. p. 621-627.

Author's Abstract

The expedition spent eight months at heights of over 15,000 ft (4,570 m). Physiological investigations were conducted over a period of five months in a prefabricated laboratory situated at 19,000 ft (5,790 m) (bar. 380 mmHg) during an attempted ascent of Mt. Makalu (27,790 ft; 8,470 m).

Data are reported on basal metabolism, muscular exercise, respiratory regulation, blood volume, haemoglobin and erythrocytes, electrocardiographic changes, nutrition, and endocrine and renal function. The exercise results include data on lung diffusion, cardiac output, and arterial O_2 saturation at 19,000 ft (5,790 m); and on O_2 intake, ventilation, and heart rate at heights up to 24,400 ft (7,430 m) (bar. 300 mmHg). At 24,400 ft (7,430 m) the maximum O_2 intake was found to be 1.4 l/min, ventilation B.T.P.S. 119 l/min, and heart rate 135 beats/min. Haldane end-expiratory gas samples taken at rest at 25,700 ft (7,830 m) (bar. 288 mmHg) had an average O_2 tension of 33 mmHg and CO_2 tension of 14 mmHg. Arterial O_2 saturations of less that 50% were observed during periods of two to three

minutes' maximum exercise at 19,000 ft (5,790 m), the average resting value being 67%.

The party appeared to acclimatize well to 19,000 ft (5,790 m), and card-sorting and other psychological tests revealed no evidence of mental impairment. However, all members of the party continued to lose weight, and this makes it doubtful if they could have stayed there indefinitely. Newcomers on Mt. Makalu, after four to six weeks' acclimatization, were, if anything, fitter and more active than men who had wintered at 19,000 ft. (5,790 m.).

Medical aspects of the expedition are described. On Mt. Makalu cases occurred of cerebral thrombosis, pulmonary infarction, acute pulmonary oedema, pneumonia, and frostbite. The ascent was made without oxygen equipment, but oxygen was available for medical treatment.

183. Pugh LGCE.

Blood volume and haemoglobin concentration at altitudes above 18,000 ft. (5500 m).
Journal of Physiology (London) 170:344-354, 1964.

Author's Abstract

1. Blood volume, haematocrit and haemoglobin concentration were followed in six subjects during prolonged acclimatization at varying altitudes up to 19,000 ft (5800 m).

2. After 18 weeks at heights ranging from 13,000 ft (4000 m) to 19,000 ft blood volume was lower than at sea level in four out of six subjects; the mean reduction being 9%. During further periods of 3-6 weeks and 9-14 weeks at (or above) 19,000 ft, blood volume rose slowly; the final mean value being 9% above the sea-level control value.

3. The fall in blood volume was associated with a reduction in plasma volume which amounted to 27%. Plasma volume subsequently rose slowly, but the final mean value was still 19% below the sea-level control value.

4. Red cell volume and total haemoglobin rose progressively, reaching mean values 49% above the sea-level control values.

5. Haemoglobin concentration rose by 30% in the first 18 weeks, and by 8% during the following 9-14 weeks.

6. According to data collected on eight expeditions to the Himalaya and Karakoram, haemoglobin concentrations in plainsmen living at 18,000 ft (5500 m) and above do not reach the values (22.9 g/100 ml.) reported in Andean natives living at 17,500 ft (5340 m). The mean value for eight parties was 20.19 g/100 ml (SD ±0.69). It was concluded that change of plasma volume is a major factor in the regulation of haemoglobin concentration under these conditions.

184. Pugh LGC and MP Ward.

Some effects of high altitude on man.
The Lancet 2:1115-1121, 1956.

Authors' Abstract

The effects of altitude experienced on three Himalayan expeditions are described. Symptoms varied with individual susceptibility, previous experience, the stages of the ascent, and time spent at a given altitude. Lassitude, weakness, breathlessness, and retardation of thought and action are the principle effects and were always present over 18,000 ft. Acute mountain sickness was not seen, although isolated acute symptoms, such as headache and vomiting, were noted.

The physical findings from examination of men coming down from great heights were essentially normal, except that 3 men suffering from exhaustion had abnormally low blood-pressure (85-80/70-60 mmHg).

Physical deterioration eventually sets in above 20,000 ft and is the more rapid and severe the greater the altitude. Partial adaptation, however, occurs initially at least up to 23,000 ft. In previous expeditions dehydration and lack of food have been important contributory factors in deterioration.

The mental effects of great altitude and their possible sequelae are described in the light of previous Everest expeditions from 1922 onwards.

The problem of how to achieve acclimatisation as quickly as possible is discussed.

185. Purshottam T, ML Pahwa and HD Brahmachari.

Effects of 6 hours hypoxic and cold exposure on urinary electrolyte and catecholamine excretion.
Aviation, Space, and Environmental Medicine 49:62-65, 1978.

Authors' Abstract

Eleven young male Indian volunteers fasted overnight and were exposed to 6 h of cold at 8^0C (I), hypoxia at 4267 m at 28^0C (II), and cold plus hypoxia of 4267 m at 8^0C (III), in a walk-in climatic chamber; excretion of some urinary constituents was measured. Urine output was significantly decreased in (II) and increased in (I) and (III). Urine pH significantly increased only in (II). Catecholamine excretion significantly increased only in (I). Ca^{++} excretion was significantly raised in (I) and (III) and lowered in (II). Na^+ excretion was significantly decreased and K^+ excretion remained unchanged in all three stress conditions. Cold seemed to be a greater stressor than hypoxia under these stated experimental conditions.

186. Raff H.

The renin-angiotensin-aldosterone system during hypoxia.
In: Response and Adaptation to Hypoxia: Organ and Organelle, edited by S Lahiri, NS Cherniach, and RS Fitzerland. New York: Oxford University Press, 1991. p.211-222.

Annotation

Purpose

A discussion of historic and mechanistic approaches for the control of aldosterone secretion during acute and chronic hypoxia in healthy humans, sheep, cats, and rats.

Methods

To begin to analyze the mechanisms, subsequent studies were brought into the laboratory. The studies described are a mixture of acute and chronic hypoxia and of normobaric and hypobaric hypoxia in the laboratory or the field. This section is organized as follows: studies on hypoxia per se are presented first; then studies using various stimulation tests (exercise, ACTH, etc.); and finally evidence for and against endogenous inhibitors of aldosterone release are described.

Results

The aldosterone response to exercise and physiological increases in ACTH may be inhibited during hypoxia. Studies in rats found hypokalemia and this confounded interpretation of the data. The lack of hypokalemia in humans and sheep, however, suggested that this is not a unifying hypothesis. The studies involved acute or chronic normobaric or hypobaric hypoxia. Regardless of these factors, the results were fairly consistent and suggested that a factor (or factors) was selectively inhibiting aldosteronogenesis during hypoxia.

Decreased aldosterone secretion during hypoxia may be due to (1) increased ANP, (2) a change in potassium balance across the zona glomerulosa cell, and/or (3) to a direct effect of low O_2 on the adrenal.

Conclusions

Curran-Everett et al. summarized the teleogical reasons for reduced aldosterone as a normal homeostatic adaptation to hypoxia. Decreases in aldosterone may help maintain potassium balance in the face of respiratory alkalosis due to hypoxia-induced hyperventilation. Decreases in aldosterone might also help to maintain sodium excretion, thereby minimizing the formation of edema. Curran-Everett et al. proposed that the decreased aldosterone may help to maintain a normal systemic transmembrane potassium distribution, a concept supported by studies in anephric humans.

It is interesting that converting enzyme inhibitors may be beneficial for treating patients with advanced COPD in whom the hypoxic inhibition of aldosterone has been overridden by the stimulatory effects of CO_2 retention. It is also of interest that captopril or ANP decreases normocapnic hypoxic pulmonary vasoconstriction. Future therapies for altitude-induced pulmonary hypertension or chronic lung disease should consider these treatments.

The suppression of aldosterone during hypoxia may be an important homeostatic component of an overall adaptation to hypoxia. A direct and specific inhibitory effect on the zona glomerulosa of the adrenal cortex may lead to a decrease in aldosterone secretion without a decrease in ACTH and cortisol, necessary for adaptation to hypoxia. Furthermore, this would allow a decrease in aldosterone without a decrease in plasma angiotensin II concentration, which may be necessary for the maintenance of peripheral vascular resistance in hypoxic states.

187. Raff H, J Shinsako and MF Dallman. Renin and ACTH responses to hypercapnia and hypoxia after chronic carotid chemodenervation. *American Journal of Physiology* 247:R412-R417, 1984.

Authors' Abstract

We studied the effect of chronic carotid body denervation on renin (plasma renin acitivity, PRA), adrenocorticotropin (ACTH), blood pressure, and hematocrit responses to acute normocapnic (arterial CO_2 partial pressure, $PaCO_2$, 35 Torr) and hypercapnic ($PaCO_2$, 65 Torr) hypoxia (arterial O_2 partial pressure, PaO_2, 31 Torr) in five anesthetized, artificially ventilated dogs. Animals were studied at least 3 days before and again at least 10 days after carotid body denervation (bilateral carotid sinus nerve resection). Increases in PRA during hypercapnic normoxia [21.8 ±6.4 ng angiotensin I (ANG I) $ml^{-1} \cdot 3\ h^{-1}$] and normocapnic hypoxia (13.3 ±4.2 ng ANG I $ml^{-1} \cdot 3\ h^{-1}$) were not attenuated by carotid body denervation. Increases in ACTH during normocapnic hypoxia (117 ±34 pg/ml) were attenuated but not eliminated by carotid body denervation; the increase in ACTH during hypercapnic hypoxia (295 ± 93 pg/ml) was not accentuated by carotid body denervation. Both the blood pressure and hematocrit responses to normocapnic and hypercapnic hypoxia were attenuated by carotid body denervation. We concluded that 1) the renin response to hypercapnia and hypoxia is not a carotid chemoreflex, 2) the ACTH response to hypoxia is partially a carotid chemoreflex, and 3) blood pressure and hematocrit responses to hypoxia are primarily carotid chemoreflexes.

188. Ramirez G, PA Bittle, M Hammond, CW Ayers, JR Dietz and GL Colice. Regulation of aldosterone secretion during hypoxemia at sea level and moderately high altitude. *Journal of Clinical Endocrinology and Metabolism* 67:1162-1165, 1988.

Authors' Abstract

The aldosterone and cortisol responses to small doses of ACTH (0.125, 0.25, 0.5, and 1.25 g) after dexamethasone administration were measured in normal subjects at sea level while breathing room air (mean O_2 saturation, 97 ±0.9%) and again while breathing hypoxic gas to lower the O_2 saturation to 90%. A population of subjects matched for age and sex adapted to 3000 meters above sea level living in Columbia, South America, was also studied (mean O_2 saturation, 94 ±0.7%). Hypoxemia, either induced at sea level or as a consequence of high altitude living, resulted in significant inhibition of aldosterone secretion after progressive administration of increasing doses of ACTH, but did not affect the cortisol response to ACTH. In addition, it was associated with higher plasma atrial natriuretic hormone levels. PRA declined only during acute hypoxemia induced at sea level and did not change during sea level normoxemia or high altitude living. Plasma sodium and potassium concentrations were no different in the three experimental conditions. We conclude that hypoxemia inhibits ACTH-stimulated aldosterone secretion and speculate that atrial natriuretic hormone may have mediated this effect.

189. Ramirez G, M Hammond, SJ Agosti, PA Bittle, JR Dietz and GL Colice. Effects of hypoxemia at sea level and high altitude on sodium excretion and hormonal levels. *Aviation, Space, and Environmental Medicine* 63:891-898, 1992.

Authors' Abstract

Acute hypoxemia at sea level is associated with decreased aldosterone secretion. This inhibition is thought to be mediated through secretion of atrial natriuretic factor (ANF). The interaction of these two hormones should result in enhanced renal salt excretion during hypoxemic conditions. This hypothesis was tested by administration of a standardized salt load to seven normal subjects during normoxemia at sea level (SL), acute hypoxemia (AH) at sea level, and high altitude (HA) (3,000 m). Urine and venous blood samples were collected and analyzed. A natriuresis and diuresis was observed only under AH conditions. It was accompanied by a decrease in plasma aldosterone levels, but did not correlate with changes in plasma aldosterone levels, ANF, or other hormones. Increased plasma renin activity (PRA) and increased norepinephrine levels were encountered at HA suggesting sympathetic nervous system activation. No change in anti-diuretic hormone

(ADH) levels with increased plasma osmolality was seen at HA. We conclude that excretion of a salt load during normobaric hypoxemia is enhanced by a decrease in plasma aldosterone levels, unrelated to changes in ANF or other hormones. The differences observed in norepinephrine, PRA, and ADH levels during HA versus AH conditions suggest that hypobaria or chronic hypoxemia may influence these hormonal responses.

190. Ramirez G, DO Pineda, PA Bittle, SJ Agosti, HA Rabb and JR Dietz.
Salt excretory capacity in natives adapted to moderate high altitude living after acute mobilization to sea level.
Aviation, Space, and Environmental Medicine 66:1063-1070, 1995.

Authors' Abstract

The sodium excretory capacity of six normal subjects born and raised at moderately high altitude (2600 m) was evaluated at high altitude (HA), and after acute mobilization to sea level (SL). The ability of these individuals to respond to an acute salt load was evaluated by infusing a volume of 100 ml • m^{-2} body surface area (BSA) of 5% sodium chloride solution over a 30-min time period in both experimental conditions. HA natives were able to excrete a significantly greater salt load at HA than at SL (41.8% vs. 31.6%, respectively, $p<0.05$) in 3 h. No changes in plasma atrial natriuretic factor (ANF) concentration were found in either experimental condition. Despite an increase in serum osmolality, no vasopressin (AVP) response was noted either at HA or SL. No correlation between serum AVP levels and urine c-AMP concentrations was found. The enhanced excretory response to a salt load at HA was not explained by the measured hormonal changes. The lack of AVP response to increased serum osmolality, both at HA and SL, in high altitude adapted subjects is presently unexplainable.

191. Reinhart WH, B Kayser, A Singh, U Waber, O Oelz and P Bärtsch.
Blood rheology in acute mountain sickness and high-altitude pulmonary edema.
Journal of Applied Physiology 71:934-938, 1991.

Authors' Abstract

The role of blood rheology in the pathogenesis of acute mountain sickness and high-altitude pulmonary edema was investigated. Twenty-three volunteers, 12 with a history of high-altitude pulmonary edema, were studied at low altitude (490 m) and at 2 h and 18 h after arrival at 4,559 m. Eight subjects remained healthy, seven developed acute mountain sickness, and eight developed high-altitude pulmonary edema. Hematocrit, whole blood viscosity, plasma viscosity, erythrocyte aggregation, and erythrocyte deformability (filtration) were measured. Plasma viscosity and erythrocyte deformability remained unaffected. The hematocrit level was lower 2 h after the arrival at high altitude and higher after 18 h, compared with low altitude. The whole blood viscosity changed accordingly. The erythrocyte aggregation was about doubled 18 h after the arrival compared with low-altitude values, which reflects the acute phase reaction. There were, however, no significant differences in any rheological parameters between healthy individuals and subjects with acute mountain sickness or high-altitude pulmonary edema, either before or during the illness. We conclude that rheological abnormalities can be excluded as an initiating event in the development of acute mountain sickness and high-altitude pulmonary edema.

192. Rennie D, R Frayser, G Gray and C Houston.
Urine and plasma proteins in men at 5,400 m.
Journal of Applied Physiology 32:369-373, 1972.

Authors' Abstract

Urine and plasma proteins were measured before, during and after ascent from 800 to 5,400 m altitude on Mount Logan in completely unacclimatized men who had made the ascent by plane in 40 min, and in acclimatized individuals who had climbed up and had lived

at 5,400 m for 6 weeks. Protein excretion rates were increased, and creatinine excretion and clearance rates decreased, with increases in plasma creatinine levels, in both groups at 5,400 m. These changes were similar and therefore independent of acclimatization and of polycythemia. There was no evidence, from clearances of proteins and of polyvinylpyrrolidone, of any change in glomerular sieving, and the character of the proteinuria was qualitatively normal. Increases in plasma protein occurred only in those in whom there was evidence of dehydration. In the unacclimatized, after abrupt ascent, transferrin levels were decreased, possibly as a means of enhancing iron supply to the developing red cells; but after acclimatization tranferrin levels rose to above normal levels.

193. Rennie D, E Marticorena, C Monge and L Sirotzky.
Urinary protein excretion in high-altitude residents.
Journal of Applied Physiology 31:257-259, 1971.

Authors' Abstract

Two-hour urine collections and venous blood samples were taken from three groups of healthy young adult males of Quechua descent, born in the high Andes and studied in their places of permanent residence. Seventeen lived in Yauricocha (4,640 m) and twenty-six in San Cristobal (4,710 m). Thirty, who had moved down to Lima (160 m) and had lived there for more than 2 years, were studied there. Urinary protein excretion rates were increased in both groups living at high altitude, compared with the Lima group. The cause was unknown. The San Cristobal group showed relatively lower creatinine clearances. The similar hypoxia and dissimilar polycythemia in the two high-altitude groups suggested that the polycythemia rather than the hypoxia was associated with the diminished creatinine clearances in the San Cristobal men. Six other high-altitude dwellers were found to have low serum total protein and raised serum creatinine levels and were therefore not included in group comparisons.

194. Rennie IDB and BI Joseph.
Urinary protein excretion in climbers at high altitudes.
The Lancet i:1247-1251, 1970.

Authors' Abstract

Early-morning specimens of urine were collected about 14 hours after the cessation of exercise from thirteen climbers on a month-long trek in the central Himalayas. All had normal 24-hour creatinine clearance rates and exercising protein excretion rates at the start of the trek, which took the expedition to just over 18,000 ft (5,550 m). It was found that the mean protein concentration in the urine correlated with the altitude at which the samples were taken. This correlation was increased when the effect of osmolar changes was removed or the protein concentration expressed as the protein/osmolar (P/O) ratio. The correlation was further increased both individually and collectively when the altitude 24 hours before sampling was considered, despite considerable individual variation both in urine concentrations and the correlations of altitude with P/O ratios. There was a time-lag before P/O ratio reflected altitude changes, this lag being greater when ascending than when descending, and being similar to the lag in onset of symptoms and signs described by other workers in acute mountain sickness. The alterations in P/O ratio with changes in altitude was not caused by variations in exercise. Moderate though not "critical" hypoxia, affecting the kidney indirectly, was a likelier cause.

195. Reynafarje C, J Ramos, J Faura and D Villavicencio.
Humoral control of erythropoietic activity in man during and after altitude exposure.
Proceeding of the Society for Experimental Biology and Medicine 116:649-650, 1964.

Authors' Abstract

The erythropoietic stimulating factor was studied in natives and newcomers to high altitude (14,900 feet). An increase was found only in the group of newcomers after 24 hours of exposure.

The possibility of the existence of an erythropoietic depressing factor is suggested from the investigation of a group of high

altitude polycythemic subjects brought down to sea level, where they were followed 72 hours, 10 days, and 20 days after arrival. Plasma obtained from them at these time periods, when injected into rats, had a depressing erythropoietic action.

196. Richalet J-P, A-M Antezana, A Bienvenu, M Marchal, J-C Souberbiel, E Cauchy, J-L Le Trong, M Déchaux, R Kacimi, V Bonaldi, K Westerterp, B Kayser and C Dubray.
Physiological factors in survival at extreme altitude.
Hypoxia and Molecular Medicine. Proceedings of the 8th International Hypoxia Symposium, edited by JR Sutton, CS Houston, and G Coates. Burlington, VT: Queen City Printers, Chapt. 22, 1993. p.235-251.

Authors' Abstract

During a scientific expedition to Mount Sajama (Bolivia), a group of ten adult subjects (4 female, 6 male) remained for 3 weeks at the altitude of 6,542 m. No severe medical problem occurred during the stay, demonstrating the possibility of acclimatization to a prolonged hypoxic environment (mean resting arterial O_2 saturation was about 69%). Aerobic performance decreased by 44% during hypoxia, without further modification during the stay. Anaerobic performance, evaluated by a 30s Wingate test, decreased by 11%. When expressed per kg of body weight (BW), aerobic power was decreased but anaerobic power was maintained at high altitude. Mean BW loss was 9% of initial BW (1 to 10.5 kg). During the stay at 6,542 m, no further modification of BW was observed. BW loss was predominant in lower limbs, and was probably due to a 46% decrease in caloric intake during the 10-day ascent period. A 25 to 27% decrease in renal blood flow, glomerular filtration rate, and proximal tubular reabsorption, evaluated by clearance methods, was observed in most subjects. In one subject suffering from severe acute mountain sickness (AMS), a large increase in glomerular filtration rate and tubular reabsorption was evidenced, probably responsible for marked water retention. After a sharp initial increase in erythropoiesis, linked to high serum erythropoietin (EPO) concentrations, some subjects showed a stable or even a decreasing hemoglobin concentration, partly because of depressed iron stores, especially in women. EPO secretion seemed to be closely linked to the intensity of proximal tubular metabolic activity. Subjects showing a high AMS score had high EPO values. The intense activation of the adrenergic system, as shown by increased plasma norepinephrine, was probably responsible for the renal vasoconstriction. A blunted cardiac chronotropic response to adrenergic activation (exercise or isoproterenol infusion) was found, as well as a 41% decrease in the density of lymphocyte beta-adrenoreceptors, but these phenomena were not exaggerated when compared with previous results obtained at 4,350 and 4,800 m. Periodic breathing was observed in all subjects (from 1 to 80% of total sleep time), which may aggravate the hypoxic stimulus. Time spent in periodic breathing was related to the hypoxic ventilatory response to hypoxia. In conclusion, exposure to an altitude of 6,542 m induced profound modifications of some physiological functions. This limitation persisted during the 3-week stay at high altitude, without further degradation. Renal function might be important to take into account when evaluating the altitude-induced variations of water balance and EPO production. Food intake deficit is a crucial factor which impairs energy balance. All data show a great variability of individual tolerance to hypoxic stress.

197. Richalet J-P, M Déchaux, A Bienvenu, J-C Souberbielle, A-M Antezana and E Cauchy.
Erythropoiesis and renal function at the altitude of 6,542 m.
Japanese Journal of Mountain Medicine 15:135-150, 1995.

Authors' Abstract

Erythropoiesis, renal function and related hormones were studied in 10 subjects (4 women, 6 men) exposed for 3 weeks at 6,542 m. Blood was withdrawn in normoxia (N), after one (H1), two (H2) and three (H3) weeks at 6,542 m for the measurement of serum erythropoietin (EPO), blood hemoglobin (Hb), plasma ferritin (FER), renin activity (PRA), norepinephrine (NE), dopamine (DA),

aldosterone (PAC), atrial natriuretic peptide (ANP), endothelin (ET), cortisol, parathormone (PTH), 25 OH-D_3 and 1.25 $(OH)_2$-D_3 concentrations. Effective renal plasma flow (ERPF), glomerular filtration rate (GFR), absolute proximal reabsorption (APR) and distal sodium reabsorption (ADR_{Na}) rates were measured by clearance methods, in N and H2. After an initial sharp increase, EPO decreased at H2 and H3. Hb increased from N to H1 and H2 and decreased from H2 to H3. Increase in EPO at H1 varied from 3- to 134-fold among individuals. Two women showed a large increase in EPO without increase in Hb. FER showed a marked decrease in H1 and H3 as compared to N. Hb was positively related to FER in hypoxia. Iron intake in food was markedly decreased during the 2 weeks of ascent, before arriving at 6,542 m. EPO was inversely related to CaO_2 and positively related to APR. The decrease in Hb from H2 to H3, in spite of high EPO, may be due to a chronically reduced iron availability as suggested by the decrease in FER favored by a low iron intake. Factors modulating the erythropoietic response to EPO in hypoxia include nutritional and sex differences, iron stores, and tubular function that determines O_2 supply to renal sensors responsible for EPO secretion. PRA and PAC were low in H1 and H3, particularly in women, in spite of high NE. There was no hypoxia-induced dissociation between PRA and PAC during exercise. DA was high in H1 and returned to normal in H3. ANP was elevated in some subjects in H1 and was low in H3. ET, cortisol and PTH increased with altitude exposure. 25 OH-D_3 was high and 1.25$(OH)_2$-D_3 was low at high altitude. ERPF, GFR, APR, and ADR_{Na} decreased in H2, except for one subject who suffered from severe acute mountian sickness and showed high intrarenal flows and low urine output. The decreased renal flow and increased filtration fraction were probably mediated by combined effects of adrenergic drive and ET release. Tubular function was not altered. Low PRA was attributed to increased blood pressure, downregulation of β-receptors, or ET release. Suppression of PAC was related to decreased PRA and increased DA. Calcium and phosphorus homeostasis was maintained, in spite of low 1.25$(OH)_2$-D_3, by elevated PTH levels. Prolonged exposure to 6,542m induced profound modifications in renal flows and related hormones, where key O_2-dependent enzymes may play an important role, leading to a new steady state compatible with homeostasis. However, the physiological impact is severe and may not be tolerated by some individuals.

198. Richalet J-P, C Rathat, A Keromes, J-P Herry, P Larmignat, M Garnier and P Pilardeau.
Plasma volume, body weight, and acute mountain sickness.
The Lancet i:525, 1983.

Authors' Abstract

During the French medical expedition to the Himalayas (Expédition Médicale Francaise en Himalaya Numbur 81) in the autumn of 1981, we measured plasma volumes on nine men aged 24-45 who normally lived at sea-level. One of them presented with signs of severe acute mountain sickness (AMS), without pulmonary oedema.

Plasma volume was measured by dye-dilution technique (Evans blue) at sea-level (SL), at 4,950 m after 1 week of activity between 4,000 and 5000 m (BC1), and at 4,950 m after 4 weeks' activity between 4000 and 7000 m (BC2). The man with AMS did not climb higher than 4,950 m (base camp altitude). Body weight was measured with a 10 g precision scale.

Plasma volume and body weight in the eight men who remained free of AMS, apart from a slight headache relieved by 1 g aspirin, are shown in the figure. The man with AMS was 45 years old and had a severe headache (resistant to 1 g aspirin), insomnia, anorexia, and slight facial oedema, but no dyspnoea at rest or crepitant ràles. Signs of right ventricular overload were noticed on an electrocardiogram. The development of AMS was certainly due to a too rapid ascent from 3,500 to 4,950 m, 2 days before the measurements at BC1. This man did not climb any higher and all signs of AMS disappeared after 3 days of bed rest.

As noted by others, plasma volume decreased at high altitude in sea-level natives. We found a 7% decrease at BC1 ($p<0.05$) and 10% decrease at BC2 ($p<0.05$); body weight falling by 3% ($p<0.001$) and 5% ($p<0.001$), respectively (Student's t test for paired data; n = 8). In contrast, in the man with AMS, plasma volume rose but had returned to a value within the range of the others for BC2; and he was the only man whose body weight rose at BC1. These findings are consistent with a water overload in AMS demonstrated here by plasma volume measurement.

If dye escapes from the vascular bed, this might artificially increase the dilution volume, but previous workers have not mentioned this problem, even in peripheral oedema.

The pathophysiology of this water balance disturbance is not clear yet, though modifications in hormonal secretions may play a role. The overload of the circulatory system may contribute to the development of pulmonary or cerebral oedema, associated with other factors such as pulmonary hypertension, alkalosis, or increase in cerebral blood flow.

The normal reaction of the human body to a high altitude environment is loss of plasma volume and body weight; abnormal acclimatisation may lead to increases in both. Body weight measurements could be an easy and cheap way to detect those at risk of severe AMS during high altitude treks or expeditions.

199. Rock PB, WJ Kraemer, CS Fulco, LA Trad, MK Malconian, MS Rose, PM Young and A Cymerman.
Effects of altitude acclimatization of fluid regulatory hormone response to submaximal exercise.
Journal of Applied Physiology
75:1208-1215, 1993.

Authors' Abstract

To determine the effect of altitude acclimatization on plasma levels of atrial natriuretic peptide (ANP) during submaximal exercise and its relationship with renin and aldosterone, seven male volunteers aged 17-23 yr exercised to exhaustion on a cycle ergometer at 80-85% of their maximum O_2 uptake at sea level (SL; 50 m), during 1 h in a hypobaric chamber [acute altitude (AA); 4,300 m], and after 14 or 16 days of residence on the summit of Pikes Peak, CO [chronic altitude (CA); 4,300 m]. Plasma samples taken before exercise, 10 min after the start of exercise, and 5 min postexercise were analyzed for ANP, plasma renin activity (PRA), and aldosterone (ALDO). ANP showed a progressive increase from rest to postexercise [7.49 ±1.63 to 11.32 ±1.80 (SE) pmol/ml and 6.05 ±2.55 to 10.38 ±7.20 pmol/ml; P = 0.049, exercise] at SL and AA, respectively, but not at CA (P = 0.039, altitude). Similarly, PRA and ALDO rose from rest to postexercise ($P<0.001$, exercise), but the rise in ALDO with exercise was less during AA than during SL and CA (P = 0.002, phase). The decreased ANP levels during exercise after altitude acclimatization, with no change in PRA and ALDO, suggest that ANP has little effect on PRA and ALDO under these conditions.

200. Rose MS, CS Houston, CS Fulco, G Coates, JR Sutton and A Cymerman.
Operation Everest II: nutrition and body composition.
Journal of Applied Physiology
65:2545-2551, 1988.

Authors' Abstract

Progressive body weight loss occurs during high mountain expeditions, but whether it is due to hypoxia, inadequate diet, malabsorption, or the multiple stresses of the harsh environment is unknown. To determine whether hypoxia due to decompression causes weight loss, six men provided with a palatable ad libitum diet, were studied during progressive decompression to 240 Torr over 40 days in a hypobaric chamber where hypoxia was the major environmental variable. Caloric intake decreased 43.0% from 3,136 to 1,789 kcal/day ($P<0.001$). The percent carbohydrate in the diet decreased from 62.1 to 53.2% ($P<0.001$). Over the 40 days of the study the subjects lost 7.4 ±2.2 (SD) kg and 1.6% (2.5 kg) of the total body weight as fat. Computerized tomographic scans indicated that most of the weight loss was derived from fat-free weight. The data indicated that prolonged exposure to the increasing hypoxia was associated with a reduction in carbohydrate preference and body weight despite access to ample varieties and quantities of food. This study suggested that hypoxia can be sufficient cause for the weight loss and decreased food consumption reported by mountain expeditions at high altitude.

201. Sánchez C, C Merino and M Figallo.

Simultaneous measurement of plasma volume and cell mass in polycythemia of high altitude.
Journal of Applied Physiology 28:775-778, 1970.

Authors' Abstract

In 13 native residents of Cerro de Pasco (4,330 m above sea level) simultaneous measurement of the red cell and plasma volumes was performed using the ^{51}Cr and the Evans' blue dye techniques, respectively. A mean value of 51.7 ±16.63 ml/kg body wt for the red cell volume and a mean value of 33.4 ± 9.44 ml/kg body wt for plasma volume were found. The fall in plasma volume in the majority of the cases had an inverse relationship with the hematocrit value, resembling the polycythemia seen in congenital heart disease.

202. Scaro JL.
Actividad eritropoyetica del extracto urinario de sujetos residentes en la altura.
Revista de la Sociedad Argentina de Biologia 36:1-8, 1960.

Authors' Abstract

The urine alcohol extracts of permanent residents in Jujuy at 1,260 m above sea level does not show erythropoietic activity when injected into the rat.

The urine extracts of new comers at high altitude show an erthyropoietic activity whose value is highly significant 48 hours after arriving at 3990 m.

The activity of urine alcoholic extracts of long time residents at high altitude is markedly lower than that of new comers two days after their arrival, but it is nevertheless markedly higher than that of residents at 1260 m.

The weight of the alcohol extract obtained from 1000 cm^3 of urine in the recently arrived residents increases proportionally with their erythropoietic activity.

203. Schmidt W, G Brabant, C Kröger, S Strauch and A Hilgendorf.
Atrial natriuretic peptide during and after maximal and submaximal exercise under normoxic and hypoxic conditions.
European Journal of Applied Physiology 61:398-407, 1990.

Authors' Abstract

The present study was designed to investigate the influence of exercise intensity and duration as well as of inspiratory oxygen content on plasma atrial natriuretic peptide concentration ([ANP]) and furthermore to compare ANP with the effect on aldosterone concentration ([Aldo]). Ten untrained male subjects performed a maximal exercise test (ME) on a cycle ergometer and a submaximal test of 60-min duration at 60% of maximal performance (SE) under normoxia (N) and normobaric hypoxia (H) (partial pressure of oxygen: 12.3 kPa). Five subjects were exposed to hypoxia at rest for 90 min. The [ANP] was mostly affected by exercise intensity (5 min after ME-N, +298.1%, SEM 39.1%) and less by exercise duration (at the end of SE-N: +229.5%, SEM 33.2%). Hypoxia had no effect at rest and reduced the exercise response (ME-H, +184.3%, SEM 27.2%; SE-H, +172.4%, SEM 15.7%). In contrast to ANP, the Aldo response was affected more by duration at submaximal level (+290.1%, SEM 34.0%) than by short maximal exercise (+235.7%, SEM 22.2%). Exposure to hypoxia rapidly decreased [Aldo] (-28.5%, SEM 3.7% after 30min, $P<0.01$), but did not influence the exercise effects (ME-H, +206.2%, SEM 26.4%; SE-H, +321.6%, SEM 51.6%). The [ANP] increase was faster than that of [Aldo] during the maximal tests and there was no difference during submaximal exercise. Changes in plasma volume (PV), sodium concentration, and osmolality (Osm) were most pronounced during maximal exercise (for ME-N: PV -13.1%, SD 3.6%, sodium +6.2 mmol $\cdot$ l^{-1}, SD 2.7, Osm +18.4 mosmol $\cdot$ kg H_2O^{-1}, SD 6.5). Regression analysis showed high correlations between changes in [ANP] and in Osm during and after maximal exercise and between changes in [ANP] and heart rate for submaximal exercise. It is concluded that, besides other mechanisms, increased Osm might be involved in the exercise-dependent increase of plasma [ANP].

204. Schmidt W, KU Eckardt, A Hilgendorf, S Strauch and C Bauer.
Effects of maximal and submaximal exercise under normoxic and hypoxic conditions on serum erythropoietin level.

International Journal Sports Medicine 12:457-461, 1991.

Authors' Abstract

This study was carried out to investigate the influence of different exercise regimens on serum immunoreactive erythropoietin concentration (EPO). The same untrained male subjects performed bouts of maximal and submaximal exercise (60 min at 60% of maximal performance) under normoxic (n = 10) and normobaric hypoxia (PIO_2 92 mmHg, n = 9). Five of them were exposed to hypoxia for 90 min under resting conditions (RTH). [EPO] was unchanged up to five hours after maximal (MEN) and submaximal (SEN) exercise under normoxia. After RTH, [EPO] increased after 3 hours by 5.0 mU/ml (p<0.01). Submaximal exercise under hypoxia (SEH) led to a similar increase in [EPO] (after 3 hours: +5.5 mU/ml), which remained elevated the following days (after 24 h: +6.1 mU/ml, 48 h: +5.3 mU/ml; ANOVA p<0.001). Maximal exercise under hypoxia (MEH) had no significant effect. The results indicate that exercise has no immediate effect on serum [EPO], whereas the higher EPO level one and two days after SEH could result from the occurring hemodilution as is indicated by a slight negative correlation between [EPO] and Hct (r = 0.59, p<0.001). The number of reticulocytes increased after all hypoxic experiments and after MEN without any correlation to [EPO].

205. Schmidt W, H Spielvogel, KU Eckardt, A Quintela and R Peñaloza.

Effects of chronic hypoxia and exercise on plasma erythropoietin in high-altitude residents.

Journal of Applied Physiology 74:1874-1878, 1993.

Authors' Abstract

The present study was performed to evaluate the effects of chronic inspiratory hypoxia and its combination with physical exercise on plasma erythropoietin concentration ([EPO]). Eight natives from the Bolivian Plateau were investigated at 3,600 m above sea level at rest, as well as during and up to 48 h after exhaustive exercise (EE) and 60 min of submaximal (60%) cycle ergometer exercise (SE). Ten sea-level subjects were used as a control group for resting values. The mean resting plasma [EPO] of the high-altitude group (19.5 ±0.7 mU/ml) did not differ from that of the sea-level group (18.1 ±0.4 mU/ml), but was higher than would be expected from the relationship between [EPO] and hematocrit at sea level. Five hours after both types of exercise, [EPO] decreased by 2.1 ±0.8 (EE, P<0.01) and by 1.6 ±0.8 mU/ml (SE, P<0.05); 48 h after SE [EPO] increased by 2.6 ±0.9 mU/ml (P<0.05). It is concluded that 1) high-altitude natives need relatively high [EPO] to maintain their high hematocrit, and 2) exercise at low basal arterial Po_2 does not directly increase plasma [EPO] in high-altitude residents but seems to exert suppressive effects.

206. Schneider EC and LC Havens.

The changes in the content of haemoglobin and red corpuscles in the blood of man at high altitudes.

American Journal of Physiology 36:380-397, 1914.

Authors' Abstract

1. At low altitudes abdominal massage increases the number of red corpuscles and percentage of haemoglobin in the peripheral capillaries. In men partially or wholly acclimatized to a high altitude, abdominal massage lowers the content of haemoglobin and red corpuscles. Before the subject reacts to the influence of lowered barometric pressure, abdominal massage may raise the content of haemoglobin and red corpuscles.

2. Physical exertion at low altitudes concentrates the blood, but during a sojourn of four days to two weeks at a high altitude this reaction occurs only in the period before the number of red corpuscles and percentages of haemoglobin have increased. In a subject who had lived five and a half months at 14,109 feet a given exercise caused a slight concentration of the blood but not as much as it did at the altitude of Colorado Springs.

3. While there is a reserve supply of corpuscles at low altitudes; this is lacking for some time during residence at the high altitude.

4. The number of red corpuscles and percentage of haemoglobin do not increase immediately on arrival at the high altitude. Usually there occurs within twenty-four hours a marked increase in both.

5. The rise in haemoglobin and red corpuscles for a particular subject during the first three or four days spent at a high altitude is not the same for different visits. The increase is most rapid in subjects who have taken regular exercise before ascending to the high altitude.

6. Fatigue due to walking up a mountain delays the altitude increase in haemoglobin and red corpuscles.

7. The rapid increase in the number of red corpuscles and percentage of haemoglobin the first two or three days spent at a high altitude is due in part to the throwing into the general circulation of a large mass of reserve corpuscles, and in part to a loss of fluid from the blood. The blood forming centers also become more active and increase the total number of corpuscles and total amount of haemoglobin.

207. Sharma SC, RS Hoon, V Balasubramanian and KS Chadha.
Urinary catecholamine excretion in temporary residents of high altitude.
Journal of Applied Physiology 44:725-727, 1978.

Authors' Abstract

Urinary catecholamine excretion was estimated in 50 lowlanders temporarily staying at altitudes above 3,000 m. They were divided in subgroups according to the length of their continuous stay. For comparison, 25 highlanders who were born and brought up at high altitude and 50 lowlanders who had never been to altitudes of more than 1,000m were also studied. High catecholamine excretion was noted in temporary residents staying at high altitude for up to 30 days, as compared to that in lowlanders (P<0.01). The excretion rate gradually returned to basal values thereafter. Catecholamines were essentially similar in lowlanders and highlanders. The significance of these finding is discussed regarding the possible pathogenetic role of the sympathoadrenal system in the development of ill effects in response to high-altitude exposure.

208. Shigeoka JW, GL Colice and G Ramirez.
Effect of normoxemic and hypoxemic exercise on renin and aldosterone.
Journal of Applied Physiology 59:142-148, 1985.

Authors' Abstract

Five subjects (group 1) performed progressive treadmill exercise on 2 separate days, once while breathing room air (normoxemc) and the other time while breathing gas with a fractional inspired O_2 of 17% (hypoxemic). Five other subjects (group 2) performed two progressive treadmill exercise tests on each of 2 separate days in a crossover design. On day 1 normoxemic exercise was first, followed by hypoxemic exercise, and on the other day the pattern was reversed. Plasma renin activity (PRA) increased to a similar extent with hypoxemic exercise as with normoxemic exercise. Plasma aldosterone concentrations (PAC) rose to a significantly higher level during normoxemic exercise than with hypoxemic exercise. Comparing changes in PRA to PAC with progressive exercise revealed dissociation of PAC from PRA during hypoxemic exercise. The PAC response remained depressed when normoxemic exercise followed hypoxemic exercise. These results indicate that hypoxemia interferes with PRA-mediated aldosterone secretions. The mechanism of this inhibition is unclear.

209. Sieker HO, OH Gauer and JP Henry.
The effect of continuous negative pressure breathing on water and electrolyte excretion by the human kidney.
Journal of Clinical Investigation 33:572-577, 1954.

Authors' Abstract

The effects of decreased intrathoracic pressure on arterial blood pressure, venous pressure, cardiac output, and pulmonary pressure and volume have been investigated in the past. The present study was prompted by the association of marked diuresis with continuous negative pressure breathing in anesthetized animals and the observation that in unanesthetized man continuous positive pressure breathing leads to an oliguria. The purpose of this investigation was to demonstrate that human subjects, like anesthetized animals, have an increased urine flow in response to continuous negative pressure breathing. Observations were made

on the renal excretion of water, sodium and potassium, urinary pH, and endogenous creatinine clearance in the hope that the mechanism of the diuresis might be elucidated.

210. Siggaard-Andersen J, FB Petersen, TI Hansen and K Mellemgaard.
Plasma volume and vascular permeability during hypoxia and carbon monoxide exposure.
Scandinavian Journal of Clinical and Laboratory Investigation 103:39-48, 1968.

Authors' Abstract

The effect on plasma volume and capillary permeability to albumin of high altitude (3,454 m) and of carbon monoxide (CO) was investigated during acute exposure (12 hours) and more prolonged exposure (8 days). Prolonged exposure to CO resulted in a decrease or no change in plasma volume, while prolonged exposure to hypoxia showed a more marked decrease in plasma volume. Acute exposure to hypoxia gave no change or a decrease in plasma volume. No changes were found in plasma volume during acute exposure to CO, although the results probably were overestimated due to an increase in capillary permeability. Capillary permeability was unchanged during exposure to hypoxia. From the present results it seems justified to conclude that CO has a more pronounced effect on the permeability of the capillaries to albumin than hypoxia alone, although the explanation for this finding could be that the tissue hypoxia was more severe in the CO experiments than during hypoxia.

211. Singh MV, SC Jain, SB Rawal, HM Divekar, R Parshad, AK Tyagi and KC Sinha.
Comparative study of acetazolamide and spironolactone on body fluid compartments on induction to high altitude.
International Journal of Biometerorology 30:33-41, 1986.

Authors' Abstract

Studies were conducted on 29 male healthy subjects having no previous experience of living at high altitude. These subjects were divided into three groups; i.e., subjects treated with placebo, acetazolamide, and spironolactone, These subjects were first studied in Delhi. The drug schedule was started 24 hour prior to the airlift of these subjects to an altitude of 3,500 m and was continued for 48 hour after arrival at high altitude. Total body water, extracellular water, plasma volume, blood electrolytes, pH, pO_2, pCO_2 and blood viscosity were determined on the 3rd and 12th days of their stay at high altitude. Total body water, extracellular water intracellular water and plasma volume decreased on high altitude exposure. There was a further slight decrease in these compartments with acetazolamide and spironolactone. It was also observed that spironolactone drives out more water from the extracellular compartment. Loss of plasma water was also confirmed by increased plasma osmolality. Increase in arterial blood pH was noticed on hypoxic exposure, but the increase was found less in acetazolamide and spironolactone cases. This decrease in pH is expected to result in better oxygen delivery to the tissues at the low oxygen tension. It was also confirmed because blood pO_2 increased in both the groups. No significant change in plasma electrolytes was observed in subjects of various groups. Blood viscosity slightly increased on exposure to high altitude. The degree of rise was found less in the group treated with spironolactone. This study suggests that both the drugs are likely to be beneficial in ameliorating/prevention of the AMS syndrome.

212. Singh I, MS Malhotra, PK Khanna, RB Nanda, T Purshottam, TN Upadhyay, U Radhakrishnan and HD Brahmachari.
Changes in plasma cortisol, blood antidiuretic hormone and urinary catecholamines in high-altitude pulmonary oedema.
International Journal of Biometeorology 18:211-221, 1974.

Authors' Abstract

In 10 subjects susceptible to high altitude pulmonary oedema (HAPO), plasma cortisol and antidiuretic hormone (ADH) and urinary catecholamines were estimated both at sea level and daily during their stay at 3,500 m (Leh). At high altitude 4 of the subjects developed HAPO, 2 got acute mountain sickness (AMS), and 4 remained unaffected. Plasma cortisol showed a sharp rise on the first day at high altitude in all the subjects. Thereafter, it declined gradually in the unaffected subjects. In the HAPO patients there was a sharp fall in the plasma cortisol level combined with antidiuresis. Changes in plasma ADH and urinary catecholamines were not consistent. It appears that failure in the normal adrenocortical response to altitude stress in susceptible subjects is a factor in precipitating HAPO.

213. Singh MV, SB Rawal, AK Tyagi, MJK Bhagat, R Parshad and HM Divekar.
Changes in body fluid compartments on re-induction to high altitude and effect of diuretics.
International Journal of Biometeorology 32:36-40, 1988.

Authors' Abstract

Studies were carried out in 29 healthy young adults in the Indian Army stationed in the plains and posted at an elevation of 3500 m for more than 6 months. After exposure to a low elevation in Delhi (260 m) for 3 weeks, they were reinduced to a height of 3,500 m. The subjects were divided into three groups, each of which was treated with either placebo or acetazolamide or spironolactone. The drug treatment was started immediately after their landing at high altitude and continued for 2 days only. Total body water, extracellular fluid, intracellular fluid, plasma volume, blood pH, PaO_2, $PaCO_2$ and blood viscosity were determined on exposure at Delhi and on re-induction to high altitude. Plasma volume was increased after the descent from high altitude and remained high for up to 21 days. This increased plasma volume may have some significance in the pathogenesis of pulmonary oedema. Total body water and intracellular fluid content were increased at 260 m elevation, while extracellular fluid decreased. On re-induction there was a decrease in total body water with no change in the extracellular fluid content.

214. Singh MV, SB Rawal and AK Tyagi.
Body fluid status on induction, reinduction and prolonged stay at high altitude on human volunteers.
International Journal of Biometeorology 34:93-97, 1990.

Authors' Abstract

Studies on adaptation to high altitude (HA) of 3,500 m in the Himalayas were conducted in three phases, each including 10 normal and healthy males normally resident at sea-level. Phase I subjects had no previous experience of HA, phase II subjects after 4-6 months at HA were airlifted to sea-level, and phase III subjects stayed continuously for 6 months at 3,500 m. Body fluid compartments and blood gases were determined in all three groups. Plasma volume was highly elevated in the phase II subjects on reinduction to sea-level from HA. In comparison to phase I subjects, the retention of fluid in the extracellular compartment was increased at HA leading to increased susceptibility to high altitude illness. Phase III subjects were hyperhydrated with decreased plasma volume and increased PO_2 in comparison to the other two groups.

215. Siri WE, C Reynafarje, NI Berlin and JH Lawrence.
Body water at sea level and at altitude.
Journal of Applied Physiology 7:333-334, 1954.

Annotation

Purpose

To elucidate changes in body water and fat in humans during and after acclimatization to low oxygen tension.

Methods

Two groups of subjects were used. The first group consisted of 15 normal young males (medical students), residents of Lima, Peru; whereas the second group consisted of 13 normal male Peruvian Indians (mine workers) living at 16,400 feet or above. Total body water was determined by the tritium dilution method and fat was determined by the formula (%fat = 100-1.37 _ %water)

Results

The mean body water and body fat for the subjects at sea level was 55.6 and 23.8%, respectively. The mean body water and body fat for subjects living at 16,400 ft was 60.6% and 17.0%, respectively. This difference in body water of about 5% was not considered as a significant effect of acclimatization, but rather suggests a slight difference in gross body composition, i.e., in the relative amount of fat and lean body mass because of the respective occupations of the two groups.

Conclusions

Total body water was determined in two groups of young, normal subjects. One group living at sea level and the other acclimatized to 16,400 ft. The mean values of body water for the two groups were normal for their age range and occupations.

216. Siri WE, DC Van Dyke, HS Winchell, M Pollycove, HG Parker and AS Cleveland.
Early erythropoietin, blood, and physiological responses to severe hypoxia in man.
Journal of Applied Physiology 21:73-80, 1966.

Authors' Abstract

Serum and urinary erythropoietin, plasma-iron turnover, and various physiological parameters were systematically measured in a human subject exposed 4 days to 405.6 mm Hg (simulated 16,400 ft) following rapid decompression. Serum erythropoietin became detectable at 12 hr, reached maximum concentration on the 3rd day, and fell to low levels on the 4th. Plasma-iron turnover and hemoglobin synthesis followed a similar pattern, although elevated rates persisted for some time after return to sea-level pressure. The rise and fall in serum erythropoietin correlated with other physiological changes occurring during acute acclimatization including marked changes in cardiac and pulmonary function, subsidence of severe hypoxic symptoms; and increased serum protein bound iodine, oxygen consumption, urinary excretion of adrenocortical steroids, and concentration of all blood cells except erythrocytes in peripheral blood. No significant changes occurred in total red cell and plasma volumes nor in the measured blood and urinary electrolyte and enzyme concentrations.

217. Slater JDH and TP Jowett.
The kidney and aldosterone in acclimatization at altitude.
British Journal of Diseases of the Chest 71:203, 1977.

Authors' Abstract

Five climbers were studied during an ascent of a 7,500 m mountain in the Hindu Kush. Representative samples from 24-hour urines were preserved from five subjects at 5,400 m and 6,600 m, and from two at 7,000 m. Sodium and cortisol excretion was normal, but that of potassium and especially aldosterone was low, especially in two climbers who had episodes of peripheral oedema. Hypoaldosteronism is a feature of high altitude acclimatization but its cause and significance have still to be elucidated.

218. Slater JDH, RE Tuffley, ES Williams, CH Beresford, PH Sönksen, RHT Edwards, RP Ekins and M McLaughlin.
Control of aldosterone secretion during acclimatization to hypoxia in man.
Clinical Science 37:327-341, 1969.

Authors' Abstract

1. Six normal men were studied under controlled conditions with a constant diet for 4-5 day periods before, during and after exposure to mild hypoxia produced by an ascent to 3500 m above sea level.

2. Aldosterone secretion fell ($P<0.05$) to 65% ±8 of mean control values on the third day at altitude and rose on descent. The rate of renal aldosterone excretion also fell.

3. Cortisol secretion rose significantly on ascent and fell slightly on descent.

4. Plasma renin activity also rose slightly on ascent and fell significantly on descent.

5. We conclude that the changes of aldosterone secretion cannot be explained in terms of known control mechanisms.

219. Slater JDH, ES Williams, RHT Edwards, RP Ekins, PH Sönksen, CH Beresford and M McLaughlin. Potassium retention during the respiratory alkalosis of mild hypoxia in man: Its relationship to aldosterone secretion and other metabolic changes. *Clinical Science* 37:311-326, 1969.

Authors' Abstract

1. Six normal men were studied under controlled conditions with a constant diet for 4-5 day periods before, during and after exposure to hypoxia induced by ascending to an altitude of 3,500 m above sea level.

2. The expected changes of plasma $PaCO_2$, bicarbonate and chloride were seen during hypoxia, but the rate of renal potassium excretion decreased to a mean of 39% ±10 of mean control values (minimal excretion second day) with a 5% increase of plasma potassium concentration. Sodium excretion fell slightly during the first 2 days at altitude but subsequently rose to 159% ±13 (maximal excretion fourth day). These changes were reversed on return to 520 m. Total solute output and free water reabsorption were almost unchanged.

3. Aldosterone secretion fell ($P<0.05$) to 65% ±8 of mean control values on the third day at altitude and rose on descent.

4. We suggest that the fall in the rate of renal potassium excretion represents an overall retention of body potassium which is mediated partly by a direct effect of extracellular alkalosis on skeletal muscle cells, and partly by a reduction in the rate of Na/K exchange in the renal tubule which we attribute to a reduction of aldosterone action.

220. Smith HP, AE Belt, HR Arnold and EB Carrier. Blood volume changes at high altitude. *American Journal of Physiology* 71:395-412, 1924.

Authors' Abstract

The effect on hemoglobin, red blood cells, hematocrit and blood volume of four weeks residence at high altitude was studied in 6 human subjects.

The red count and hemoglobin rise almost proportionately throughout, reaching in 3 weeks a maximum of 10 to 15 per cent above the sea level value.

The percentage of red blood cells (hematocrit) rises somewhat less indicating that the individual cells are slightly smaller though capable of holding the same amount of hemoglobin.

There is no evidence of abrupt changes in red blood cells or blood volume within the first day or two spent at high altitude.

Blood volume determinations by the dye and by the carbon monoxide methods indicate that the rise in red cells and hemoglobin is due to the production of more cells, not to a redistribution.

221. Sobrevilla LA and F Salazar. High altitude hyperuricemia. *Proceedings of the Society for Experimental Biology and Medicine* 129:890-895, 1968.

Authors' Abstract

Fifteen normal male and 15 normal female subjects living permanently at a mining town located at an altitude of 14,000 ft HA in the central Andean plateau demonstrated elevation of the values of serum urate, creatinine, and hematocrit when compared with equal numbers of normal subjects living at sea level (SL). Of the HA male group, three subjects (20%) had urate values above 8 mg/100 ml, the level at which urate deposition in tissues might take place. There was a high degree of correlation between the serum urate levels and the hematocrit and between the serum creatinine and the hematocrit in the series as a whole. Although the mean hematocrit values of the HA females and the SL males were comparable, the latter had higher urate levels, reflecting the influence of sex on urate levels.

222. Stenberg J, B Ekblom and R Messin. Hemodynamic response to work at simulated altitude of 4,000 m. *Journal of Applied Physiology* 21:1589-1594, 1966.

Authors' Abstract

Oxygen uptake, pulmonary ventilation, cardiac output (dye-dilution technique), blood pressure (intra-arterial), oxygen content of arterial blood, and blood lactic acid concentration were determined in six men, 19-36 years of age, during submaximal and maximal work on a bicycle ergometer at sea level and after 10-60 min exposure to P_B 462 mmHg in an altitude chamber (simulated altitude 4,000 m, 13,115 ft). With the arterial oxygen saturation reduced from 96 to 70%, maximal oxygen uptake was reduced to 72% of that at sea level; i.e., 3.46 and 2.50 liters/min, respectively. Maximal values for pulmonary ventilation were 118 and 124 liters/min, cardiac output 23.2 and 23.7 liters/min, heart rate 184 and 186 beats/min, stroke volume 126 and 127 ml, $(A\text{-}V)O_2$ diff 108 and 146 ml at simulated altitude and at sea level, respectively. Integrated mean arterial blood pressure was lower during work in hypoxia. At submaximal work the heart rate, cardiac output, and pulmonary ventilation were significantly elevated during hypoxia. Moderate acute hypoxia does not seem to interfere with cardiac performance or the tissues' capability to extract oxygen from the blood during exercise.

223. Stokke KT, K Rootwelt, R Wergeland and JR Vale.

Changes in plasma and red cell volumes during exposure to high altitude. *Scandinavian Journal of Clinical and Laboratory Investigation* 46:113-117, 1986.

Authors' Abstract

Training at moderate altitude has been used by athletes to improve their performance at sea level. Not all athletes benefit from altitude training, and there also has been some doubt as to whether red cell volume increases in all subjects. Ten members of the Norwegian Everest Expedition 1985 took part in the present study. Plasma volume was determined by isotope dilution using ^{125}I-albumin. By simultaneous measurement of hematocrit, the total blood volume and red cell volume were calculated. Measurements were done in Oslo (sea level) before departure, and in Base Camp (5300 m) four weeks later. The mean altitude during these four weeks was 4100 m. Red cell volume increased in all participants, and excessively in two of them. Since plasma volume decreased in four subjects, the change in total blood volume was less consistent. In one climber dehydration led to a decrease in total blood volume. While a significant correlation was found between maximal oxygen uptake and red cell volume at sea level, the hematologic response to altitude seemed independent of physical fitness. In one climber the erythropoietic response was so excessive (more than 50% increase in red cell volume), that he had to be hemodiluted.

224. Sundstroem ES.

Studies on adaptation of man to high altitudes: V. Effect of high altitudes on salt metabolism with special reference to the mechanism of maintaining the acid-base equilibrium of the body. *University of California Publications in Physiology* 5:121-132, 1919.

Author's Abstract

1. By computing the intake and output of acids and bases on a uniform diet in terms of decinormal solutions in a case of successful acclimatization to an elevation of 3,100 m, an increase of the base output was found. This excess elimination of bases was caused by an increased output of fixed alkalies.

2. In a case of mountain sickness, at an altitude of 4,300 m, the increase of base excretion was delayed.

3. This excessive output of bases cannot be attributed to an excretion of lactates, since the excretion of lactic acid remained of normal dimensions.

4. It is suggested that the excessive base output was partly due to elimination of bicarbonates, and partly to salts of strong fatty acids.

5. The decrease of ammonia output is explained as a corollary to the increase in the elimination of fixed alkalies.

6. The increase of base excretion is considered to be the main mechanism in restoring the reaction of the blood, disturbed by the loss of carbon dioxide.

7. The possibility that decrease of acid output may be an auxiliary mechanism in maintaining the acid-base equilibrium is considered.

8. It is pointed out that the "Zuntz phenomenon" may also participate in bringing about adaptation to high altitudes.

225. Surks MI.
Metabolism of human serum albumin in man during acute exposure to high altitude (14,100 feet).
Journal of Clinical Investigation 45:1442-1451, 1966.

Author's Abstract

The metabolism of human serum albumin was studied by means of albumin-^{131}I in five young males at 5,280 feet, and for 8 days at 14,100 feet altitude. The data were analyzed in a manner that made possible the daily estimation of the rate of albumin degradation and synthesis + net transfer from the extravascular to intravascular compartments.

Albumin degradation was increased markedly for 24 to 48 hours within the first 3 days at high altitude. A large shift of high specific activity albumin from the extravascular to intravascular compartments occurred towards the end of altitude exposure and was accompanied by a decrease in the rate of albumin synthesis + net transfer.

A decrease in the intake of calories and protein (minimum – 0.90 g per kg per day), as well as a negative nitrogen balance, was observed during the high altitude period.

The data are discussed in relation to changes in thyroid and adrenocortical function that have been observed in this environment.

226. Surks, MI.
Elevated PBI, free thyroxine, and plasma protein concentration in man at high altitude.
Journal of Applied Physiology 21:1185-1190, 1966.

Author's Abstract

Various aspects of thyroxine binding by plasma proteins have been studied in eight sea-level residents before, during, and after 28 days exposure to 14,100 ft altitude. Mean plasma concentration of protein-bound iodine, total protein, and the binding capacity of thyroxine-binding globulin were elevated within 3 days, reached a maximum after 9 days, and returned toward low-altitude values between 12-15 days at altitude. They reached control levels within 4 days after descending to sea level. In spite of an increased intensity of thyroxine binding by plasma proteins, the concentration of plasma free thyroxine was increased at altitude. Since the electrophoretic distribution of plasma proteins was unaltered, plasma dehydration in the initial phase of altitude exposure was concluded to be responsible for most of the observed alterations in thyroxine binding. A decrease in mean binding capacity of thyroxine-binding prealbumin is interpreted to reflect changes in protein synthesis and/or degradation which may also occur in this environment.

227. Surks MI, HJ Beckwitt and CA Chidsey.
Changes in plasma thyroxine concentration and metabolism, catecholamine excretion and basal oxygen consumption in man during acute exposure to high altitude.
Journal of Clinical Endocrinology 27:789-799, 1967.

Authors' Abstract

Plasma total and free thyroxine concentration, thyroxine turnover, catecholamine excretion and basal oxygen consumption were measure in 5 young male subjects during a control period at 5280 feet altitude and for 8 days at 14,100 feet (Pikes Peak, Colorado). Turnover data were analyzed in a manner enabling the calculation of daily rates of thyroxine degradation during the experimental period. Thyroxine degradation was increased during the first 3 days at high altitude and thereafter remained slightly elevated. Mean basal oxygen consumption increased from 125 to 147 ml per min per m^2 on the first day at high altitude and then progressively decreased toward the control value. Plasma total and free thyroxine concentration and norepinephrine excretion were not altered during the first 2 days at altitude, but then increased continually for the remainder of altitude exposure. Epinephrine and total metanephrine excretion were unchanged, but the increased sympathetic activity was reflected by an increase in the excretion of vanillymandelic acid. The temporal association between the initial hypermetabolism and increased thyroxine degradation at altitude suggests that these changes may be causally related. The later

alterations in sympathetic activity and circulating thyroxine concentrations may play a role in the adaptation to more prolonged exposure to this environment.

228. Surks MI and JE Canham.
Albumin metabolism in man at high altitude.
Federation Proceedings 25:399, 1966. (Abstract).

Authors' Abstract

The turnover of injected I-131 albumin was studied in 5 young males during a 10-day control period at 5,280 altitude and for 8 days at the summit of Pikes Peak, Colorado (14,110 ft). The control mean fractional degradation rate of plasma I-131-albumin (plasma K) was 0.1182 ±0.0031 per day which resulted in the degradation of 16.07 ±0.80 g albumin per day. A marked increase in plasma K occurred during the first 3 days of high altitude exposure. Thereafter, mean plasma K remained 10-20% higher than the control. The amount of albumin degraded during altitude exposure, however, was less than that anticipated by alterations in plasma K because of a reduction in the intravascular (Iv) albumin pool. Analysis of extravascular (Ev) and plasma specific activity curves initially showed no increase in the rate of synthesis +Ev net to Iv transfer of albumin. In the last several days of altitude exposure albumin synthesis +Ev to Iv transfer was reduced. These observations were correlated with a voluntary decrease in caloric and protein intake and a concomitant negative nitrogen balance.

229. Surks MI, KSK Chinn and LRO Matoush.
Alterations in body composition in man after acute exposure to high altitude.
Journal of Applied Physiology 21:1741-1746, 1966.

Authors' Abstract

Body composition was measured in five young males, residents of Denver, Colorado (5,280 ft altitude) before, during, and after 8 days on the summit of Pikes Peak, Colorado (14,100 ft altitude). Body weight progressively decreased during the altitude period resulting primarily from a decrease in body fat as estimated by measurements of body density, creatinine excretion, and total body potassium (K) (from K^{40} counting). No changes were observed in total body water (W), lean body mass, protoplasmic mass (M_3), and bone mineral, all of which were derived from the same measurements. Although M_3 was unchanged, calculations based on creatinine excretion and K showed an increase in nonmuscle protein at the expense of muscle protein. Attempts to measure W directly, employing deuterium oxide dilution, were unsuccessful possibly due to uneven distribution of this isotope in the body water compartments at high altitude. A highly significant decrease (P<0.001) in plasma volume after 4 and 8 days at altitude provided direct evidence for altered water distribution in this environment.

230. Sutton JR, GW Viol, GW Gray, M McFadden and PM Keane.
Renin, aldosterone, electrolyte, and cortisol responses to hypoxic decompression.
Journal of Applied Physiology 43:421-424, 1977.

Authors' Abstract

Responses of plasma renin activity, plasma aldosterone, plasma cortisol, and plasma electrolyte concentration, and urinary electrolyte and aldosterone excretion, were studied in four men during hypoxic decompression to a simulated altitude of 4,760 m in a pressure chamber. Three of the four subjects developed significant acute mountain sickness. Plasma sodium and potassium concentrations were unchanged. No significant change in plasma renin activity was observed, but the values tended to fall. Plasma aldosterone concentration was depressed, while plasma cortisol was elevated and diurnal variation lost. Urinary sodium excretion was unchanged, but urinary potassium and aldosterone excretion were decreased. The decrease in plasma and urinary aldosterone and urinary potassium, in the absence of change in plasma renin activity or plasma potassium, is of uncertain origin. It is unlikely to be due to a decrease in adrenocorticotropin secretion since plasma cortisol rose during the same time. None of the changes could be causally implicated in the development of acute mountain sickness, although the increase in plasma cortisol was greatest in the most ill.

231. Swenson ER, TB Duncan, SV Goldberg, G Ramirez, S Ahmad and RB Schoene.

Diuretic effect of acute hypoxia in humans: relationship to hypoxic ventilatory responsiveness and renal hormones.

Journal of Applied Physiology 78:377-383, 1995.

Authors' Abstract

Acute hypoxia causes increased sodium and water excretion. Animal studies suggest that this renal response is largely driven by direct peripheral arterial chemoreceptor stimulation, independent of accompanying changes in ventilation and acid-base status. Whether the diuresis and natriuresis observed in humans made acutely hypoxic are caused by peripheral chemoreceptor stimulation is not known, but if so, we hypothesized that people with a high ventilatory response to hypoxia (high peripheral chemosensitivity) should have greater diuresis and natriuresis than those with a low ventilatory response to hypoxia. The isocapnic hypoxic ventilatory response (HVR) of 16 subjects on a fixed sodium intake was measured, as were their urinary volumes and sodium and bicarbonate losses during 6 h of breathing air (in a normobaric environmental chamber) and, on the subsequent day, 12% O_2. The isocapnic HVR correlated positively with hypoxic diuresis (r = 0.87) and natriuresis (r = 0.76). In contrast, the isocapnic HVR did not correlate with bicarbonate excretion despite the expected respiratory alkalosis of acute hypoxia. The magnitude of diuresis and natriuresis with hypoxia did not correlate with changes in circulating aldosterone, renin, atrial natriuretic peptide, vasopressin, or a digoxin-like immunoreactive substance. These findings are compatible with a role of the peripheral arterial chemoreceptors in mediating the renal response to hypoxia in humans. The efferent pathway remains unknown.

232. Thurau K.

Renal Na-reabsorption and O_2-uptake in dogs during hypoxia and hydrochlorothiazide infusion.

Proceedings of the Society for Experimental Biology and Medicine 106:714-717, 1961.

Annotation

Purpose

To decrease active reabsorption of sodium and oxygen consumption in the kidney by means of low arterial oxygen pressure or administration of hydrochlorothiazide; to determine the Na/net O_2 ratio under these conditions when tubular load and renal blood flow were essentially unchanged; and to gain information about basal renal oxygen consumption under the influence of hypoxia or hydrochlorothiazide.

Methods

Twelve normal hydrated mongrels were anesthetized with nembutal (9 dogs) or with inactin (3 dogs), and renal oxygen consumption and sodium reabsorption were determined during hypoxia and under the influence of hydrochlorothiazide.

Results

In hypoxia (arterial O_2 saturation 35%) less sodium was reabsorbed and renal O_2 consumption was diminished. Urine volume was increased with a decrease in U/P_{OSM}, U/P_{creat}, and T^c_{H20}. During administration of hydrochlorothiazide both sodium reabsorption and O_2 consumption were lowered. Urine volume and C_{OSM} were elevated, U/P_{OSM} and U/P_{creat} decreased while $T^c_{H^2O}$ remained unchanged. Plotting Na reabsorption (eq/g min) against O_2 consumption (mol/g min) resulted in a straight line which intercepted the O_2 consumption axis at 1 mol/g min. This value may be equated with renal basal O_2 consumption; i.e., without Na reabsorption. The O_2 requirement for renal sodium reabsorption was calculated to be 28.6-33 eqNa/ mol O_2.

Conclusions

The data suggest that active sodium reabsorption and net oxygen consumption in the dog kidney can be lowered proportionately during severe hypoxia. Because the alterations caused by hypoxia were abolished 20 minutes after the dogs were again breathing room-air makes it unlikely that hormonal influences were involved. Although it cannot be determined with certainty, the decrease in T^c_{H2O} may be caused by a decrease of active sodium reabsorption in the medulla by hypoxia. The basal oxygen consumption of 1 mol/g kidney min is not affected by hypoxia or hydrochlorothiazide.

233. Timiras PS, N Pace and CA Hwang.
Plasma and urine 17-hydroxycortico-steriod and urine 17-ketosteroid levels in man during acclimatization to high altitude.
Federation Proceedings 16:340, 1957. (Abstract).

Authors' Abstract

Studies were made on 6 healthy adult males during the summer of 1955. The subjects went from their residence in Berkeley (250 ft) to the Barcroft Laboratory (12,470 ft) of the White Mountain Research Station for 3 separate sojourns of 5-8 days each with intervening periods at sea level. All urine was collected throughout successive 12-hr periods for 1-3 days in the week preceding each exposure and every day at altitude. Venous blood specimens were obtained before breakfast. After exposure to altitude, urinary excretion of 17-hydroxycorticosteroids and of 17-ketosteroids was increased by as much as 300% and 50%, respectively, over sea level values. Similarly, plasma levels of 17-hydroxycorticosteroids were higher at altitude than at sea level with a maximum increase of 115%. On the other hand, the urine and plasma levels of adrenocortical hormones and their metabolites appeared to be related to the duration of the exposure and the degree of acclimatization. They rose during the first 3 days of each sojourn at altitude and then returned toward the sea level values. In addition, the magnitude of these changes decreased in successive sojourns. The observations suggest that exposure to altitude stimulates in man adrenocortical activity but that the increase in the levels of the adrenocortical hormones is only temporary.

234. Torres C, R Lozano, J Whittembury and CC Monge.
Effect of angiotensin on the kidney of the high altitude native.
Nephron 7:489-498, 1970.

Authors' Abstract

Renal hemodynamics, sodium and water excretion were studied in six sea level residents and eight high altitude (4,500 m) natives before, during and after the infusion of small amounts of angiotensin (0.32 g/min). In basal conditions the high altitude group showed a mild reduction in the glomerular filtration rate, with a higher reduction in the renal plasma flow and a normal or slightly increased renal blood flow. During angiotensin infusion, both sea level and high altitude groups responded with a marked reduction in urine flow and sodium excretion. The glomerular filtration rate and renal plasma flow diminished, with a greater fall in the latter. These changes were smaller in the high altitude group, except in the sodium to inulin clearance ratio, which was similar in both groups. Despite a high filtration fraction, the kidney of the high altitude native responds to angiotensin like the sea level kidney. These results are discussed in relation to the paradoxical renal response to angiotensin observed in the hypertensive patient.

235. Tucker A, JT Reeves, D Robertshaw and RF Grover.
Cardiopulmonary response to acute altitude exposure: water loading and denitrogenation.
Respiration Physiology 54:363-380, 1983.

Authors' Abstract

In order to determine if a positive water balance would impair cardiovascular and ventilatory adjustments during acute altitude exposure, six healthy male subjects were exposed to 4570 m for 2 h with and without water loading. No significant differences in any of the measured variables were observed between normal and overhydrated subjects. In order to determine if rapid ascent to altitude involves the formation of nitrogen bubbles which could impair gas exchange, 11 subjects were exposed to 4,570 m with and without denitrogenation (by breathing 100% O_2 prior to ascent) and 6 subjects were exposed to normobaric hypoxia (14% O_2). Prior O_2 breathing reduced their hyperventilatory and alkalotic responses to altitude, tachycardia did not develop, and systemic blood pressure fell, despite the fact that arterial desaturation was similar to that during the untreated altitude exposure. Reduced urine flow and increased urine osmolality were observed in two subjects at 4,570 m, but these changes were not observed in the same subjects after O_2

breathing. Breathing 14% O_2 also produced the same degree of arterial desaturation, but the hyperventilatory response was significantly greater than in the prior altitude exposures. Heart rate, blood pressure, and urine flow and osmolality were not altered and symptoms of altitude illness were minimal. Thus, neither of our hypotheses proved to be correct; however, we did observe a prolonged effect of O_2 breathing on the hypoxic ventilatory response, and a potential effect of hypobaria on ventilation.

236. Tuffley RE, D Rubenstein, JDH Slater and ES Williams.
Serum renin activity during exposure to hypoxia.
Journal of Endocrinology 48:497-510, 1970.

Authors' Abstract

Changes of serum renin activity, heart rate, blood pressure, renal sodium, potassium and metadrenaline excretion, and alveolar gas tensions were recorded during two 2-3 h exposures to 446 mmHg barometric pressure (simulated altitude of 4,279 m or 14,000 ft). Serum renin activity rose considerably during the first exposure and only slightly during the second. This effect was positively correlated with the changes of heart rate. There was little change in blood pressure or in the rate of renal excretion of sodium, potassium or the metadrenalines.

It is suggested that the change of serum renin activity cannot be explained by a direct effect of hypoxaemia, emotion, posture or the diurnal rhythm of renin secretion, but that it may be correlated with changes of cardiovascular function.

237. Tunny TJ, J van Gelder, RD Gordon, SA Klemm, SM Hamlet, WL Finn, GM Carney and C Brand-Maher.
Effects of altitude on atrial natriuretic peptide: the bicentennial Mount Everest Expedition.
Clinical and Experimental Pharmacology and Physiology 16:287-291, 1989.

Authors' Abstract

1. Overnight recumbent atrial natriuretic peptide levels were significantly elevated in all ten subjects of the Australian Bicentennial Mount Everest Expedition during the first week at 5,400 m during acclimatization.

2. Twenty-four hour urine volume and urine sodium increased markedly at altitude.

3. Plasma renin activity and plasma aldosterone levels decreased significantly at altitude.

4. No significant changes in plasma cortisol, plasma sodium or potassium, body temperature, systolic or diastolic blood pressure or heart rate were observed.

5. Although it was impossible to control or measure salt and water intake during the study, results suggest that atrial natriuretic peptide may be important for the reduction in renin and aldosterone levels and in the diuresis and natriuresis necessary to adapt to hypoxia at altitude.

238. Ullmann EA.
Renal water and cation excretion at moderate altitude.
Journal of Physiology (London) 58-59, 1953. (Abstract).

Author's Abstract

Water and sodium metabolism were studied in one healthy subject during 12 days in London, 29 days on the Jungfraujoch (11,340 ft, B.P. around 500 mmHg), and a further 14 days in London. No symptoms of altitude sickness were experienced at any time.

Voluntary or anoxic hyperventilation of short duration at sea-level leads to an immediate increase in renal sodium, potassium and water output; water diuresis is markedly accelerated; urinary pH rises and ammonia and titratable acid excretion fall.

By contrast, during the first 2 days on the Jungfraujoch water sodium and potassium excretion were strongly depressed. A positive sodium balance of +240 m.equiv and water retention of 1.5 l. developed in 48 hr. On the second day a test dose of water produced almost no diuretic response. Urinary pH remained low, but ammonia and titratable acid outputs were below mean London values.

The need for fixed base excretion asserted itself on the third day when a sodium diuresis began which lasted for 3 days. The daily sodium balance became negative (mean 42 m.equiv/day) and water and weight was lost in spite of a high calorie intake. Relatively more

sodium than water was eliminated. Potassium excretion recovered more slowly.

From the 6th to the 29th day no further significant disturbance of water balance occurred. Titratable acid and ammonia excretion remained low, and only rose again after return to sea-level.

Mean daily sodium output for the rest of the period at altitude was slightly below the London mean; a slight but increasing sodium retention developed from the 11th day onwards. Serum sodium remained unchanged during the entire period of observation.

From the 7th day on the Jungfraujoch onward renal potassium excretion increased progressively, both absolutely (London mean: 61 m.equiv/day; Jungfraujoch, 8th-29th day, mean 89 m.equiv/day), and relatively, as a fraction of total cation excretion. The increased output stopped abruptly on return to London.

In the absence of data showing potassium balance, the possibility that the increased loss reflects increased intake cannot be ruled out, but this is unlikely. Together with the observed changes in sodium metabolism, the finding suggests a possible increase in adrenocortical activity at altitude. The diuretic response to ingested water was more rapid on the Jungfraujoch than at sea level. The adrenal cortex may be implicated here also.

The stimulus for the initial inhibition of water and fixed base excretion cannot be attributed to anoxia or alkalosis, but was probably due to some non-specific factor connected with change of environment; perhaps acting through release of antidiuretic hormone from the posterior pituitary. This is suggested by the fact that exactly the same sequence of events occurred on return to sea level. In this case, however, water and sodium retention were prolonged beyond the 3rd day.

239. Ullmann E.

Acute anoxia and the excretion of water and electrolyte.
Journal of Physiology (London) 155:417-437, 1961.

Author's Abstract

1. A study was made of the effects of acute anoxic anoxia with and without concomitant hypocapnia on the volume and composition of the urine of healthy human adults.

2. The respired gas mixtures contained 14-8% oxygen, usually approximately 10%. Exposure to anoxia lasted one hour.

3. The excretion of sodium, potassium, bicarbonate and chloride increased, and the ratio of (H^++NH_4^+) ions to (Na^++K^+) ions decreased if anoxia was accompanied by hypocapnia.

4. If during anoxia the development of hypocapnia was carefully prevented, only trivial alterations in urinary solute output were found.

5. In most experiments anoxia led to polyuria and enhanced the diuresis following ingestion of water. This could only in part be attributed to a rise in solute excretion, since it occurred equally in the presence and absence of hypocapnia; i.e. of large and small changes in solute output. The findings were consistent with the hypothesis that in acute anoxia the basal rate of secretion of antidiuretic hormone (ADH) may be diminished.

6. If anoxia caused distress the subjects rapidly became oliguric. This appeared to be the result of a sudden discharge of ADH from the neurohypophysis.

7. Fainting during anoxia was followed by profound oliguria and longlasting, specific depression of sodium excretion.

8. The changes in renal excretion which were associated with hyperpnoea, hypocapnia, distress and the vasovagal syndrome in anoxia were the same as those which accompany these extra-renal disturbances if they arise from causes other than systemic oxygen lack. It appeared therefore that the intrinsic responses of the nephrons to those agents which modify their excretory and regulatory function were not defective in anoxia.

240. van Beaumont W and JE Greenleaf.

Effect of hyperhydration on working men at sea level and simulated altitude.
Federation Proceedings 30:427, 1991. (Abstract).

Authors' Abstract

Overhydrated men working in the heat have lower heart rates and rectal temperatures than normohydrated men (Moroff and Bass, J. Appl. Physiol. 20:267, 1965). Few additional data on the influence of hyperhydration on work performance are available. In the present series of experiments, 3 men worked at 32%,

64%, and 100% of max $\dot{V}O_2$ at sea level and simulated altitude. When the men were kept hyperhydrated with a water load equal to 2% of their body weight; oxygen consumption, ventilation and respiratory rates were similar at all work levels and atmospheric pressures compared to normohydration. Hyperhydration reduced the heart rates during submaximal work at 3,000 meters. During diuresis at sea level and altitude, urine flow was not reduced during work of 32% max $\dot{V}O_2$. During work rates of 64% max $\dot{V}O_2$, urine flow was progressively reduced in spite of expanded blood volumes and normal plasma osmolarities. Apparently exercise greater than 35% max $\dot{V}O_2$ has a direct effect on the renal fluid retention mechanism.

241. Vuolteenaho O, P Koistinen, V Martikkala, T Takala and J Leppäluoto.
Effect of physical exercise in hypobaric conditions on atrial natriuretic peptide secretion.
American Journal of Physiology 263:R647-R652, 1992.

Authors' Abstract

To evaluate the role of atrial natriuretic peptide (ANP) in exercise-related cardiovascular and hormonal adjustments in hypobaric conditions, 14 young athletes performed a maximal ergometer test in a hypobaric chamber adjusted to simulate the altitudes of sea level and 3,000 m. Plasma immunoreactive ANP levels rose from 5.89 to 35.1 pmol/l at sea level and rose significantly less ($P<0.05$), from 5.36 to 22.3 pmol/l, at simulated 3,000 m. Plasma immunoreactive amino-terminal peptide of proANP (NT-proANP) levels increased to the same extent at sea level and at simulated 3,000 m (from 240 to 481 pmol/l and from 257 to 539 pmol/l, respectively). Plasma immunoreactive aldosterone increased significantly less at simulated 3,000 m ($P<0.05$), but the changes in plasma renin were similar in both conditions. Plasma immunoreactive endothelin-1 and serum erythropoietin levels remained unchanged. In conclusion, we found a blunted ANP response to maximal exercise of ANP in acute hypobaric exposure compared with that in normobaric conditions, but no significant difference in the NT-proANP responses between the two conditions. The divergence may be due to stimulation of the elimination mechanism of ANP.

242. Wang JM, AR Whang and DE Smith.
Preoperative water deficits at 4,945 feet above sea level.
Rocky Mountain Medical Journal 65:35-39, 1968.

Annotation

Purpose

To assess the magnitude of water losses sustained by the hydroapenic, preoperative patient at 4,945 feet.

Methods

Observations of preoperative water deficits were made on seven afebrile, ambulatory patients and on two afebrile, ambulatory control subjects during the months of October and November in Albuquerque, New Mexico situated at 4,945 feet above sea level. All subjects were weighed at 9 p.m. the night prior to surgery (wt. #1). No food or fluid was permitted during the subsequent 10 hours of sleep. Urine losses were collected and measured at the end of the 10 hour study period. Fecal losses were nil at 7 a.m.; ten hours after the initial weighing the subjects were re-weighed (wt. #2). Water deficits incurred during the 10 hour study period were calculated as the difference in weight (wt. #1 wt. #2) giving the net loss in weight from which was subtracted the urinary volume.

Results

Water losses during the 10 hour study period in preoperative patients average 641 milliliters and 495 milliliters in the control subjects. Based on these measured losses, the estimated 24-hour water deficits approximated 1,539 ml and 1,188 ml, respectively. Based upon an estimated endogenous production of water of 270 ml per day, the final derived estimation of 24-hour insensible water loss was 1,269 ml for the preoperative patients and 918 ml for the control subjects.

Conclusions

Observations of preoperative water deficits were made in Albuquerque, New Mexico situated at 4,945 feet above sea level. The mean preoperative deficits in seven patients were 641 ml measured over a 10-hour period study period. The estimated net 24-hour insensible water losses approximate 1,269 ml.

243. Weil JV, DJ Battock, RF Grover and CA Chidsey.
Venoconstriction in man upon ascent to high altitude: studies on potential mechanisms.
Federation Proceedings 28:1160-1164, 1969.

Annotation

Purpose

To make observations of the venous circulation together with measurements of hematocrit and plasma volume following arrival at high altitude to determine whether changes occur which might be expected to raise capillary pressure and hence cause the decreased plasma volume generally seen under these circumstances.

Methods

Forearm venous compliance was measured in eight normal male residents of Denver, Colorado (1,600 m) in May 1967 before they were transported by automobile to the summit of Pikes Peak (4,300 m). Serial studies of venous compliance beginning within 2 hr of arrival were continued over 24 hr at high altitude in each subject by using a water-filled plethysmograph. Hematocrit, plasma volume (T1824), and 24-hr urinary vanillymandelic acid (VMA) excretion were also measured in Denver and on Pikes Peak.

Results

Venous compliance during the control period averaged 2.76 ±0.087 (SEM) ml/100 ml. Changes by 9 hr at high altitude were 17.0 ±6.2% reduction in venous compliance ($P<0.05$). Arterial blood gases at that time were: $PaCO_2$ 29.7 ±1.2, PaO_2 43.8 ±1.4, and pH 7.48 ±0.01. Normal Denver blood gases were: $PaCO_2$ 35.6 ±0.57, PaO_2 69 ±1.2, pH 7.42 ±0.004. Venoconstriction was sustained for the remainder of the 24 hr observation. Hematocrit and plasma volume were not affected significantly during this period and urinary VMA excretion was also unchanged.

Conclusions

Ascent to high altitude (4,300 m) causes a decrease in venous compliance in man. This venoconstriction is sustained for at least 24 hr following arrival at high altitude and appears to precede changes in plasma volume. Additional studies indicate that administration of a low oxygen gas, which produces hypoxia of a similar degree to that at Pikes Peak, does not cause venoconstriction if hypocapnia is prevented by addition of CO_2 to inspired gas. However, when hypoxia is associated with hypocapnia, venoconstriction occurs. Hypoxia of greater intensity than that seen at 4,300 m produces venoconstriction in the absence of hypocapnia. Hypocapnia appears to enhance this response.

244. Westendorp RGJ, AN Roos, M Simons, W Wertheim, FH Bosch, M Frölich and AE Meinders.
Effects of hypoxia and atrial natriuretic peptide on aldosterone secretion in healthy subjects.
Journal of Applied Physiology 75:534-539, 1993.

Authors' Abstract

To evaluate the inhibitory effect of hypoxia and atrial natriuretic peptide (ANP) on aldosterone secretion, 11 healthy male subjects were infused with 5 $ng \cdot kg^{-1} \cdot min^{-1}$ ANP or placebo. The subjects were exposed in a stepwise fashion to incremental hypobaric hypoxia, which decreased arterial oxygen saturation to 79 ±2% in the placebo and 84 ±2% in the ANP condition ($P<0.05$). In the placebo condition, the plasma ANP concentration increased from 13.8 ±1.0 to 19.6 ±2.3 pmol/l ($P<0.01$) at the lowest barometric pressure. Plasma renin activity did not change, whereas the plasma aldosterone levels increased consequent to the increase of plasma adrenocorticotropic hormone (ACTH). Continuous infusion of ANP increased the plasma levels twofold ($P<0.001$) and the level of guanosine 3',5'-cyclic monophosphate threefold ($P<0.001$). However, the plasma aldosterone concentrations were not different in the two experimental conditions. Administration of supplementary oxygen significantly decreased ACTH to baseline values ($P<0.01$) together with a decrease in aldosterone. Free water clearance ($P = 0.05$) but not sodium excretion ($P =$ NS) increased during continuous ANP infusion. The data indicate that the aldosterone secretion in hypoxia is not inhibited by (patho)physiological plasma ANP levels. The inhibition of aldosterone secretion may well be explained by a direct effect of hypoxia on the adrenal cells. ACTH is a major stimulus of aldosterone secretion in hypoxia, which overrides the natriuretic effect of ANP.

245. Westerterp KR, B Kayser, F Brouns, JP Herry and WHM Saris.
Energy expenditure climbing Mt. Everest.
Journal of Applied Physiology 73:1815-1819, 1992.

Authors' Abstract

Weight loss is a well-known phenomenon at high altitude. It is not clear whether the negative energy balance is due to anorexia only or to an increased energy expenditure as well. The objective of this study was to gain insight into this matter by measuring simultaneously energy intake, energy expenditure, and body composition during an expedition to Mt. Everest. Subjects were two women and three men between 31 and 42 yr of age. Two subjects were observed during preparation at high altitude, including a 4-day stay in the Alps (4,260 m), and subsequently during four daytime stays in a hypobaric chamber (5,600-7,000 m). Observations at high altitude on Mt. Everest covered a 7- to 10-day interval just before the summit was reached in three subjects and included the summit (8,872 m) in a fourth. Energy intake (EI) was measured with a dietary record, average daily metabolic rate (ADMR) with doubly labeled water, and resting metabolic rate (RMR) with respiratory gas analysis. Body composition was measured before and after the interval from body mass, skinfold thickness, and total body water. Subjects were in negative energy balance (-5.7 ±1.9 MJ/day) in both situations, during the preparation in the Alps and on Mt. Everest. The loss of fat mass over the observation intervals was 1.4 ±0.7 kg, on average two-thirds of the weight loss (2.2 ±1.5 kg), and was significantly correlated with the energy deficit ($r=0.84$, $P<0.05$). EI on Mt. Everest was 9-13% lower than during the preparation in the Alps. ADMR was at a high level (13.6 ±1.7 MJ/day). The activity level, expressed as ADMR/RMR, was 2.2 ±0.3 and 2.2 ±0.1, on the basis of measured and predicted RMR values, respectively. The results from this study illustrate the problems of maintaining energy balance while climbing at high altitude. EI is low, whereas energy expenditure reaches values comparable to those of highly trained endurance athletes at sea level.

246. Westerterp KR, B Kayser, L Wouters, J-L Le Trong and J-P Richalet.
Energy balance at high altitude of 6,542 m.
Journal of Applied Physiology 77:862-866, 1994.

Authors' Abstract

Weight loss due to malnutrition and possibly intestinal malabsorption is a well-known phenomenon in high-altitude climbers. Up to 5,000 m, energy balance may be attained and intestinal energy digestibility remains normal. To see whether 1) energy balance may also be attained at 6,542 m and, if not, 2) whether decreased energy digestibility would play a significant role in the energy deficit, energy intake (EI), energy expenditure, body composition, and energy digestibility of 10 subjects (4 women, 6 men; 27-44 yr) were assessed during a 21-day sojourn on the summit of Mt. Sajama, Bolivia (6,542 m). EI was measured during two 3-day intervals: EI1 (days 7-9) and EI2 (days 17-19). Total fecal energy loss during EI1 was calculated from fecal energy measured by bomb calorimetry. Average daily metabolic rate (ADMR) at altitude was measured in six subjects (2 women, 4 men) using doubly labeled water over a 10-day interval (days 9-19). Basal metabolic rate was measured before and after the expedition by respiratory gas analysis. Body composition was estimated from skinfolds and body mass before and during the altitude sojourn. Subjects were in negative energy balance throughout the observation period (EI1 ADMR = -2.9 ±1.8 MJ/day and EI2 ADMR = -2.3 1.8 MJ/day based on a gross energy digestibility of 95%). The activity level, expressed as ADMR to basal metabolic rate, was 1.56-2.39. The loss of fat mass (3.7 ±1.5 kg) represented 74 ±15% of the loss of body mass. Energy content of the feces was 21 kJ/g dry wt, and gross energy digestibility amounted to 85%. The energy deficit increased to 3.5 MJ/day after correction for the decreased energy digestibility. In conclusion, energy balance was not attained at 6,542m. The resulting energy deficit appeared to result mostly from malnutrition, and only a limited part could be attributed to malabsorption.

247. Westerterp KR, P Robach, L Wouters and J-P Richalet.
Water balance and acute mountain sickness before and after arrival at high altitude of 4,350 m.
Journal of Applied Physiology 80:1968-1972, 1996.

Authors' Abstract

The present study is a first attempt to measure water balance and its components at altitude by using labeled water and bromide dilution and relating the results with acute mountain sickness (AMS). Water intake, total water output, and water output in urine and feces were measured over a 4-day interval before and a subsequent 4-day interval after transport to 4,350 m. Total body water and extracellular water were measured at the start and at the end of the two intervals. There was a close relationship between energy intake and water intake, and the relationship was unchanged by the altitude intervention. Subjects developing AMS reduced energy intake and water intake correspondingly. The increase in total body water (TBW) in subjects developing AMS was accompanied by a reduction in total water loss. They did not show the increased urine output, compensating for the reduced evaporative water loss at altitude. Subjects showed a significant increase in TBW after 4 days at altitude. Subjects with AMS showed the biggest shifts in extracellular water relative to TBW. In conclusion, fluid retention in relation to AMS is independent of a change in water requirements due to altitude exposure. Subjects developing AMS were those showing a fluid shift of at least 1 liter from the intracellular to the extracellular compartment or from the extracellular to the intracellular compartment.

248. Whitten BK, JP Hannon, GJ Klain and KSK Chinn.
Effects of high altitude (14,100 ft) on nitrogenous components of human serum.
Metabolism 17:360-365, 1968.

Authors' Abstract

Serum free amino acids and nitrogenous metabolites were measured in 8 male subjects exposed to a high altitude of 14,100 feet for 14 days. The ratio of total essential amino acids to total nonessential amino acids was decreased at altitude. Glutamic acid increased and leucine, lysine, valine, and threonine decreased significantly at altitude. The nitrogenous metabolites taurine and urea were elevated at altitude. Serum water content increased slightly; i.e., about 1 per cent, and therefore changes in the nitrogenous components of serum at altitude cannot be explained by a dehydration effect. Alterations in serum free amino acid and nitrogenous metabolite concentrations in serum of subjects at 14,100 feet closely parallel changes in these serum components reported in subjects on protein deficient diets; however, protein intake at altitude was well above minimum requirements. This suggests that the changes in nitrogenous components of serum noted in 8 male subjects exposed to a high altitude of 14,100 feet are due to alterations in protein metabolism which affect protein utilization.

249. Williams ES.
Electrolyte regulation during the adaptation of humans to life at high altitude.
Proceedings of the Royal Society of London Series B 165:266-280, 1966.

Author's Abstract

Studies related to the body's regulation of its sodium and potassium content have been made on a number of occasions during periods spent at high altitude. It is shown that on ascent from usual levels of residence the ratio of sodium to potassium in the saliva tends to rise above normal and later to fall with continued residence at altitude. The implications of this finding have been confirmed by subsidiary studies.

The urinary aldosterone excreted while resident at altitude has been assayed and it has been shown to fall to very low levels. In contrast to what occurs with 17-hydoxycorticosteroids, there appears to be a delay in the fall of urinary aldosterone although this has still to be confirmed by further studies which, are in course of preparation. With continued residence at high altitude the urinary aldosterone level recovers, but complete recovery takes several weeks.

Published data are reviewed and it is concluded that these results are due to the changes in intravascular volume which occur on ascent to an environment of reduced pO_2. It is probable that the significant volume changes are intrathoracic.

250. Williams ES, MP Ward, JS Milledge, WR Withey, MWJ Older and ML Forsling.
Effect of the exercise of seven consecutive days hill-walking on fluid homeostasis.
Clinical Science 56:305-316, 1979.

Authors' Abstract

1. The effect of 7 consecutive days of strenuous exercise, hill-walking, on water balance and distribution was studied in five subjects. The exercise was preceded and followed by 3 control days. The diet was fixed throughout but water was allowed ad libitum.

2. Packed cell volume was measured daily. Serum electrolytes and arginine vasopressin were measured twice daily. Daily water, sodium and potassium balances were calculated.

3. During exercise there was a fall in packed cell volume, reaching a maximum of 11% by day 5, and a retention of sodium reaching a cumulative maximum of 358 mmol by day 6. During and immediately after exercise there was a retention of potassium, reaching a total of 120 mmol by day 3 after stopping exercise.

4. There was a loss of 650 ml of water on day 1 of exercise, followed by a modest retention reaching a cumulative maximum of 650 ml on day 5 of exercise.

5. Neither arginine vasopressin nor serum electrolyte concentrations were affected by exercise.

6. From the packed cell volume and sodium and water balances, it was calculated that by day 5 of exercise there was an increase in plasma volume of 0.68 litre (22%), an increase in interstitial fluid volume of 2.0 litres (17%), and a decrease in intracellular fluid volume of 1.8 litres (8%).

7. These changes, together with the clinical observation of facial and ankle oedema during the experiment, suggest that continuous exercise may cause oedema and thus may be a factor in the aetiology of high-altitude oedema.

251. Wolfel EE, MA Selland, RS Mazzeo and JT Reeves.
Systemic hypertension at 4,300 m is related to sympathoadrenal activity.
Journal of Applied Physiology 76:1643-1650, 1994.

Authors' Abstract

Residence at high altitude has been associated with elevation in systemic arterial blood pressure, but the time course has been little studied and the mechanism is unknown. Because plasma epinephrine (E) and norepinephrine (NE) also increase at altitude, we hypothesized that heightened sympathoadrenal activity may cause increased arterial pressure. We measured ambulatory blood pressure by cuff monitor in relation to 24-hour urinary excretion of E and NE at sea level and during 3 wk of residence at 4,300 m (Pikes Peak, CO) in 11 healthy men. In five subjects taking placebo, arterial pressure progressively increased at 4,300 m from 82 ±1 (SE) mmHg at sea level to 88 ±3 on day 2, 91 ±3 on day 8, and 97 ±6 on day 17. In six subjects propranolol (240 mg/day) decreased pressure from 85 ±4 to 77 ±1 mmHg at sea level, but did not prevent sustained increase in pressure at 4,300 m (84 ±1, 81 ±1, and 85 ±3 mmHg on days 2, 8, and 17, respectively). Compared with the placebo group, blood pressure did not increase further over the initial elevation observed on day 2 in the propranolol group. There was interindividual variability in the blood pressure responses in both groups, with some subjects demonstrating a more marked increase in blood pressure. Urinary excretion of NE increased concomitantly with pressure at altitude in both groups, with a greater rise in the placebo group. Blood pressures were related to NE excretion in the placebo ($r=0.67$, $P<0.005$) and propranolol groups ($r=0.47$, $P<0.05$), and subjects with the highest blood pressures at 4,300 m had the greatest NE values. Mean urinary E levels did not increase over time in the placebo group and increased only minimally at day 17 in the propanolol group. Despite this lack of increase in E at 4,300 m, arterial pressure was related to urinary E levels in the placebo (r=0.75, P<0.005) but not the propranolol group. Thus, elevation in systemic arterial pressure at 4,300 m was related to increased sympathetic activity from NE. The possibility that E also contributed to the rise in arterial pressure could not be excluded.

252. Young PM, MS Rose, JR Sutton, HJ Green, A Cymerman and CS Houston.
Operation Everest II: plasma lipid and hormonal responses during a simulated ascent of Mt. Everest.
Journal of Applied Physiology 66:1430-1435, 1989.

Authors' Abstract

To examine the effect of hypobaric hypoxia on plasma lipid profiles, fasting blood samples were collected from six men (21-31 yr) at 760 Torr and periodically during a 40-day exposure to decreasing barometric pressure culminating in a final ambient pressure of 282 Torr. Preascent plasma total cholesterol concentration ([TC]) was decreased by 25% after the 40-day exposure (P<0.01). High-density lipoprotein concentrations (HDL-C]) decreased 32% (P<0.001) with no alteration in the TC-toHDL-C weight ratio. Plasma triglyceride concentration increased twofold during this period (P<0.01). There were no significant differences in fasting plasma free fatty acid concentrations or free fatty acid-to-albumin molar ratio throughout the study. Fasting plasma insulin levels were increased approximately twofold with no significant changes in glucagon concentration or the insulin-to-glucagon molar ratio. Plasma norepinephrine concentrations were increased threefold on reaching 282 Torr (P<0.01), with no significant changes in plasma epinephrine concentrations. Mean energy intake (kcal/day) decreased 42%, whereas mean body weights decreased by 8.9 ±0.8% (P<0.01) with exposure. Increased concentrations of insulin may lead to increased hepatic production of triglyceride-rich lipoproteins, thus eliciting metabolic changes independent of weight loss and dietary intake.

253. Zachariah T, SB Rawal, SN Pramanik, MV Singh, S Kishnani, H Bharadwaj and RM Rai.
Variations in skinfold thickness during de-acclimatisation and re-acclimatisation to high altitude.
European Journal of Applied Physiology 56:570-577, 1987.

Authors' Abstract

Skinfold thickness, body weight, body water, anthropometric measurements and segment volumes were determined in 28 young and healthy Indian soldiers on return to Delhi (200 m) after staying for more than 24 months at high altitude (3500 m). The measurements were made on the 2nd day and after 3 weeks. Ten subjects were then randomly selected from this group and returned by air to the high-altitude station, and the measurements were repeated on the 3rd and 12th day of their reinduction.

Though body weight and total body water increased marginally on transfer to the lower altitude, body density remained more or less unchanged. There were significant increases in the thickness of skinfolds, even when body density had increased. During this period hand and foot volumes decreased significantly. Despite significant increases in thoracic skinfold thickness, the torso volume decreased slightly. On returning to high altitude the soldiers lost body weight, were hypohydrated and showed reduced skinfold thickness. Fat losses calculated on the basis of reduction in skinfold thickness were far in excess of those calculated from losses in body weight and in total body water. As the reduced skinfold thickness was unrelated to changes in body water content at high altitude, it seems that such reductions are due to redistribution of blood in the skin.

From the results of these investigations it is concluded that variations in skinfold thickness during acclimatisation to high altitude do not accurately represent the changes in body fat content.

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This compendium includes abstracts and synopses of clinical observations and of more basic studies involving physiological mechanisms concerning interaction of water metabolism and fluid compartment volumes in humans during altitude exposure. If the author's abstract or summary was appropriate, it was included. In other cases a more detailed synopsis of the paper was prepared under the subheadings Purpose, Methods, Results, and Conclusions. Author and subject indices are provided, plus an additional selected bibliography of related work of those papers received after the volume was being prepared for publication. This volume includes material published from 1914 through 1995.

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